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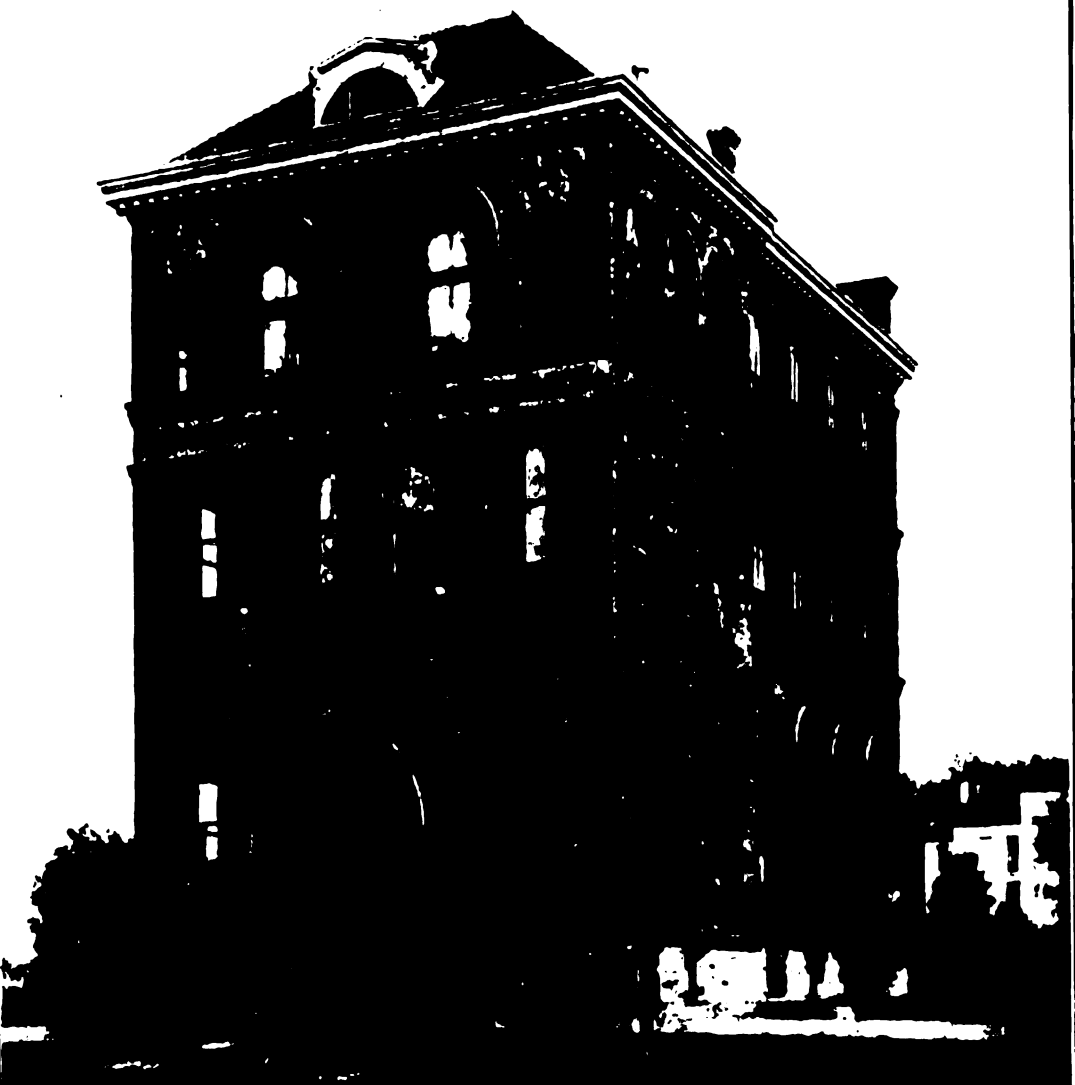

Studies from the Bender Hygienic Laboratory

Bender Hygienic Laboratory, Albany, N.Y.

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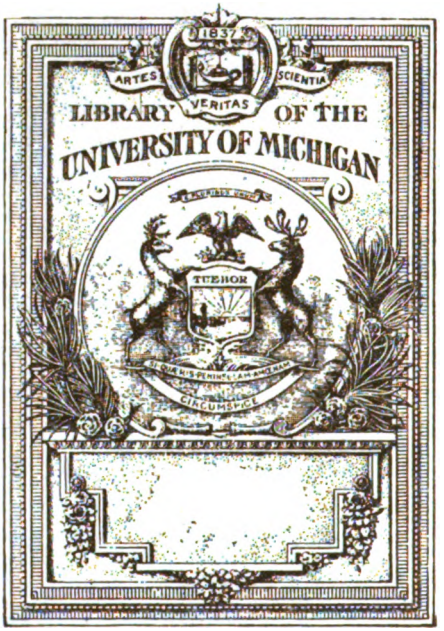

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STUDIES

FROM

THE BENDER

HYGIENIC LABORATORY

ALBANY, N. Y.

REPRINTS

VOLUME I

1904

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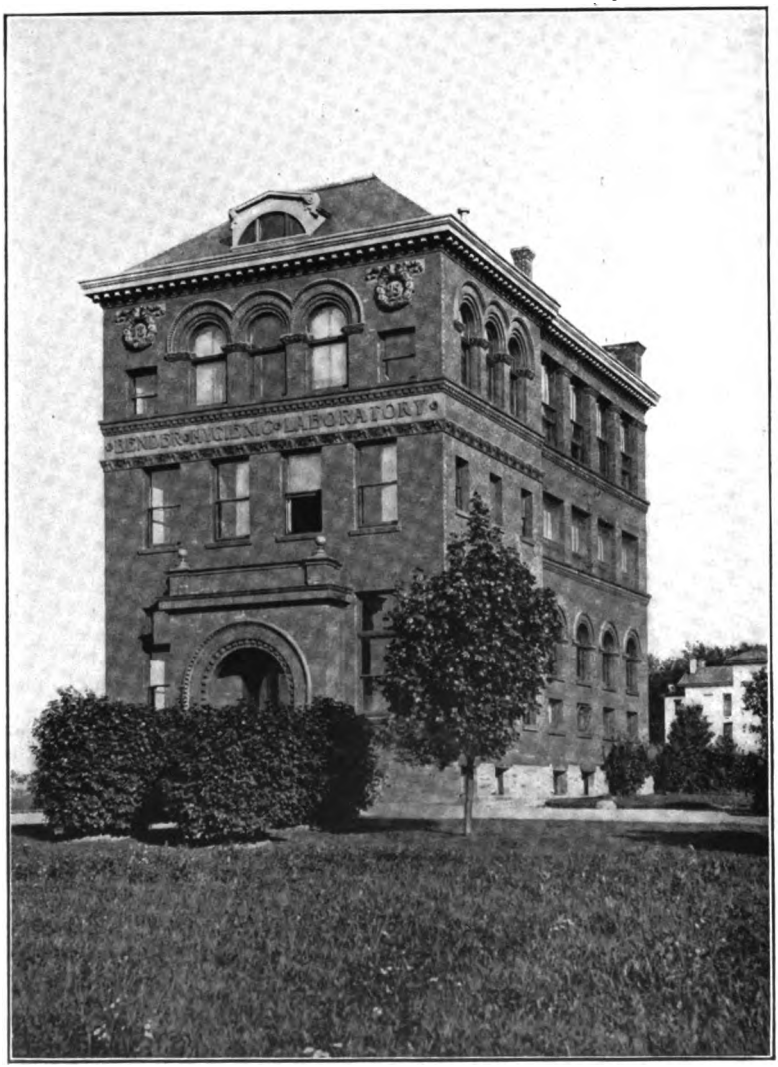

THE BENDER HYGIENIC LABORATORY

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The Organization of the Laboratory

◆ ◆ ◆

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Dr. GEORGE E. GORHAM — Hon. ROBT. G. SCHERER
HARRY H. BENDER

Director

RICHARD M. PEARCE, M.D.

Assistants

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Assistant Chemist and Bacteriologist
(In charge of the Albany Filtration Plant)

LEONARD M. WACHTER

Voluntary Assistants

ELLICE MCDONALD, M.D., 1903-'04
EDWIN F. SIBLEY, M.D., 1904-'05

In Connection with the Laboratory Courses of the Albany Medical College

RICHARD M. PEARCE, M.D., *Professor of Pathology and Bacteriology*
E. MACD. STANTON, M. D., *Lecturer in Normal Histology and in the Anatomy of the Nervous System*
ARTHUR W. ELTING, M.D., *Lecturer in Surgical Pathology*
ARTHUR T. LAIRD, M.D., *Lecturer in Clinical Microscopy*
HERBERT D. PEASE, M.D., *Lecturer upon Antitoxins and Immunity*
CHARLES K. WINNE, Jr., M.D., *Instructor in Bacteriology*
H. JUDSON LIPES, M.D., *Instructor in Obstetrical Pathology*
HARRY W. CAREY, M.D., *Instructor in Surgical Pathology*
EDWIN F. SIBLEY, M.D., *Instructor in Clinical Microscopy*
DONALD BOYD, M.D., *Demonstrator of the Anatomy of the Nervous System and Assistant in Normal Histology*

Stenographer

Miss MAUDE MARSHALL

Preparator

Miss HELEN R. KING

Janitor

J. E. G. ROY

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NOTE

THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1903-'04. These have appeared in various medical journals, but for the sake of uniformity in paper and press work, the reprints have been taken from the Albany Medical Annals. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work. As this is the first attempt to establish an annual publication, which shall adequately represent the work of this institution, a short historical sketch of the origin and development of the laboratory, with a list of previous publications, has been included.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *November*, 1904.

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RICHARD M. PEARCE, M.D.

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RICHARD M. PEARCE, M.D.

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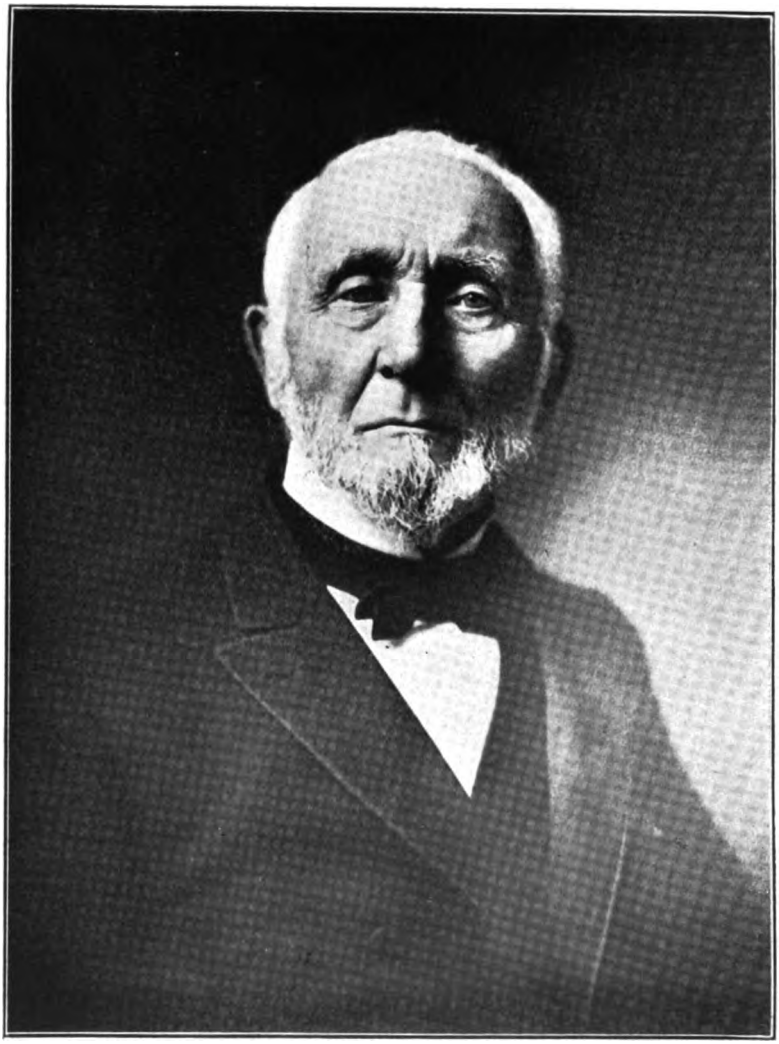

MATTHEW W. BENDER

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Reprinted from ALBANY MEDICAL ANNALS, November, 1904

HISTORY OF THE BENDER HYGIENIC LABORATORY

By GEORGE E. GORHAM, M. D.

On June 27th, 1895, the corporation of the Bender Hygienic Laboratory was formed, the members being: Mr. Matthew W. Bender, Dr. Albert Vander Veer, Dr. George E. Gorham, Dr. Henry Hun and Hon. Robert G. Scherer.

The corporation was organized to take over from Mr. Bender twenty thousand dollars, a sum which Mr. Bender had offered to give for the erection of a laboratory building upon the condition that a suitable site be furnished. The board of trustees was immediately elected, and to its care were entrusted the generous gift of Mr. Bender and the carrying out of his wishes in securing a suitable site and erecting the building. A grant from the city of Albany for the spacious and beautiful grounds on Lake avenue now occupied by the laboratory was promptly obtained. Messrs. Fuller and Wheeler were employed as architects, and under the special supervision of Mr. Harry H. Bender the building was completed and dedicated on October 27th, 1896.

Dr. George Blumer, of the Johns Hopkins Hospital, was appointed director and under his supervision the laboratory was fully equipped with necessary apparatus. About one hundred microscopes, necessary tables, lockers, etc., were placed in the class rooms; steam and hot air sterilizers, microtomes, thermostats, freezing apparatus, etc., were added for general pathological and bacteriological work.

This generous outlay for the equipment of the laboratory was furnished by the faculty of the Albany Medical College. Such, briefly, is the history of the conception and birth of the Bender Hygienic Laboratory. Sixteen months from the time the subject was first presented to Mr. Bender for his consideration by his family physician the building was completed, and opportunity for one of the most important scientific works in the history of Albany was given.

The first director of the laboratory, Dr. George Blumer, and his assistants, Dr. Lartigau, Dr. Elting, Dr. Carey and Dr. Laird,

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under the direction of the Albany Medical College, arranged and carried out a course of instruction in pathology, bacteriology, histology and microscopy for the students of the Albany Medical College. These valuable courses of instruction are continued throughout each college year. They are, in fact, part of the regular curriculum of the Albany Medical College, and classes of forty or fifty students take the different courses annually. Dr. Blumer resigned in 1903, and the work has been continued by his successor, Dr. Richard M. Pearce, assisted by Drs. Stanton and Winne.

The Albany filtration plant for filtering Albany's water supply is under supervision of the laboratory, and daily examinations of the water are made.

By special contract with the city of Albany cultures from all cases of suspected diphtheria are examined and reported to the attending physician. Sputum from suspected cases of tuberculosis is also examined. Work of the same character is done for the State Department of Health of New York.

The examination of milk and water supplies in case of epidemics throughout the State is a part of the work done at the laboratory.

Hundreds of examinations of pathological specimens, blood, sputum and urine are annually made for the hospitals of Albany, while physicians in the surrounding country are constantly sending specimens for examination.

Added to this general work of the laboratory is special research work, some forty papers having been published during Dr. Blumer's directorate, and eleven during the past year by the present staff.

Thus may be sketched in a few words the scope of the work of the Bender Laboratory. But these words indicate only inadequately the importance of this institution and the great value for years to come of the gift of Mr. Bender in promoting the health and welfare of the community.

LIST OF PUBLICATIONS FROM THE BENDER HYGIENIC LABORATORY, FROM 1896 TO 1903.

GEORGE BLUMER, M. D.

1—Diseases Which Can be Directly Traced to Contaminated Drinking Water, ALBANY MEDICAL ANNALS, March-April, 1897.

2—Primary Round Cell Sarcoma of the Epididymis, ALBANY MEDICAL ANNALS, December, 1897.

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3—Adeno-myoma of the Round Ligament, *American Journal of Obstetrics*, no. 1, 1898.

4—Tuberculosis of the Stomach, ALBANY MEDICAL ANNALS, March, 1898.

5—A System of Classification of Pathological Material, ALBANY MEDICAL ANNALS, November, 1898.

6—A Case of Post-typhoid Boné Inflammation Due to the Colon Bacillus, *The Pacific Record of Medicine and Surgery*, November 15, 1898.

7—Tuberculosis of the Aorta, *American Journal of the Medical Sciences*, January, 1899.

8—A Case of Mixed Puerperal and Typhoid Infection, *American Journal of Obstetrics*, no. 1, 1899.

9—The Present Status of the Widal Reaction, ALBANY MEDICAL ANNALS, January, 1899.

10—A Third Case of Tuberculosis of the Aorta, ALBANY MEDICAL ANNALS, May, 1899.

11—The Relation of Trauma to Tuberculosis, ALBANY MEDICAL ANNALS, November, 1899.

12—The Infectious Character of Tuberculosis and the Prognosis of Incipient Consumption, ALBANY MEDICAL ANNALS, April, 1900.

13—Hæmorrhagic Infection in an Infant Due to the Typhoid Bacillus, *Journal of the American Medical Association*, December 29, 1900.

14—Bilateral Cholesteatomatous Endotheliomata of the Choroid Plexus, *Welch's Festchrift*, 1900.

15—Further Notes on Abnormalities of the Urinary System, ALBANY MEDICAL ANNALS, January, 1901.

16—The Bacteriology of Lobar Pneumonia Especially in Adults, ALBANY MEDICAL ANNALS, August, 1901.

17—The Present Status of the Infectious Theory of Malignant Neoplasms, *New York State Journal of Medicine*, November, 1901.

18—Some Aspects of the Pathology of the Pancreas, *Medical News*, August 9, 1902.

19—A Note on the Embryonal Glandular Tumors of the Kidney, ALBANY MEDICAL ANNALS, August, 1903.

20—The Relation of the Status Lymphaticus to Sudden Death, etc., *Johns Hopkins Hospital Bulletin*, October, 1903.

With W. H. HAPPEL, M. D.

21—A Case of Pulmonary Tuberculosis Associated with Round Ulcer of the Stomach, ALBANY MEDICAL ANNALS, December, 1898.

With L. H. NEUMAN, M. D.

22—Report of a Family Outbreak of Trichinosis, *American Journal of the Medical Sciences*, January, 1900.

With A. J. LARTIGAU, M. D.

23—A Report of Three Cases of Ascending Urinary Infection Due to Bacillus Pyocyaneus and the Proteus Vulgaris, *New York Medical Journal*, September 22, 1900.

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With A. T. Laird, M. D.

24—Hæmorrhagic Infection Due to the Bacillus Mucosus Capsulatus, *Johns Hopkins Hospital Bulletin,* February, 1901.

With W. Kirk, Jr., M. D.

25—A Case of Periostitis of the Seventh Rib Occurring During the Course of Typhoid Fever, Albany Medical Annals, January, 1901.

With J. M. Mosher, M. D.

26—Hyperplasia of the Pituitary Body with Eburnation of the Skull. Albany Medical Annals, March, 1901.

With A. MacFarlane, M. D.

27—Report of an Epidemic of Noma, *American Journal of the Medical Sciences,* November, 1901.

With H. L. K. Shaw, M. D.

28—A Case of Appendicitis in an Infant Seven Weeks of Age, *Archives of Pediatrics,* August, 1901.

With H. C. Gordinier, M. D.

29—A Case of Chronic Lymphatic Leukæmia Without Enlargement of the Lymph Nodes, *Medical News,* October 31, 1903.

August J. Lartigau, M. D.

30—The Bacillus Pyocyaneus as a Pathogenic Factor in Human Pathology, with Report of Three Cases, *Philadelphia Medical Journal,* September 17, 1898.

31—A Contribution to the Study of the Pathogenesis of B. Pyocyaneus, with Especial Reference to its Relation to an Epidemic Dysentery, *Journal of Experimental Medicine,* 1898, vol. III, no. 6.

32—A Contribution to the Study of the Micrococcus Tetragenus in Acute Angina, *Philadelphia Medical Journal,* April 22, 1899.

33—On Typhoid Septicæmia, with the Report of Two Cases, one of Which was a Typhoid Infection Without Intestinal Lesions, *Johns Hopkins Hospital Bulletin,* April, 1899.

34—Typhoid Infection of the Uterus, *New York Medical Journal,* June 16, 1900.

With A. MacFarlane, M. D.

35—Acute Angina Due to Micrococcus Tetragenus, *Journal of the American Medical Association,* June 24, 1899.

With H. C. Gordinier, M. D.

36—A Report of a Case of Typhoid Pleurisy, *American Journal of the Medical Sciences,* January, 1901.

Arthur W. Elting, M. D.

37—The Acute Pneumonic Form of Tuberculosis, *American Journal of Medical Sciences,* May, 1900.

38—The Bacteriology of Gonococcus Infections, Albany Medical Annals, March, 1900.

39—Intermittent Gastric Hypersecretion, *Boston Medical and Surgical Journal,* May, 1900.

40—Primary Carcinoma of the Vermiform Appendix, with a Report of Three Cases, *Annals of Surgery,* April, 1903.

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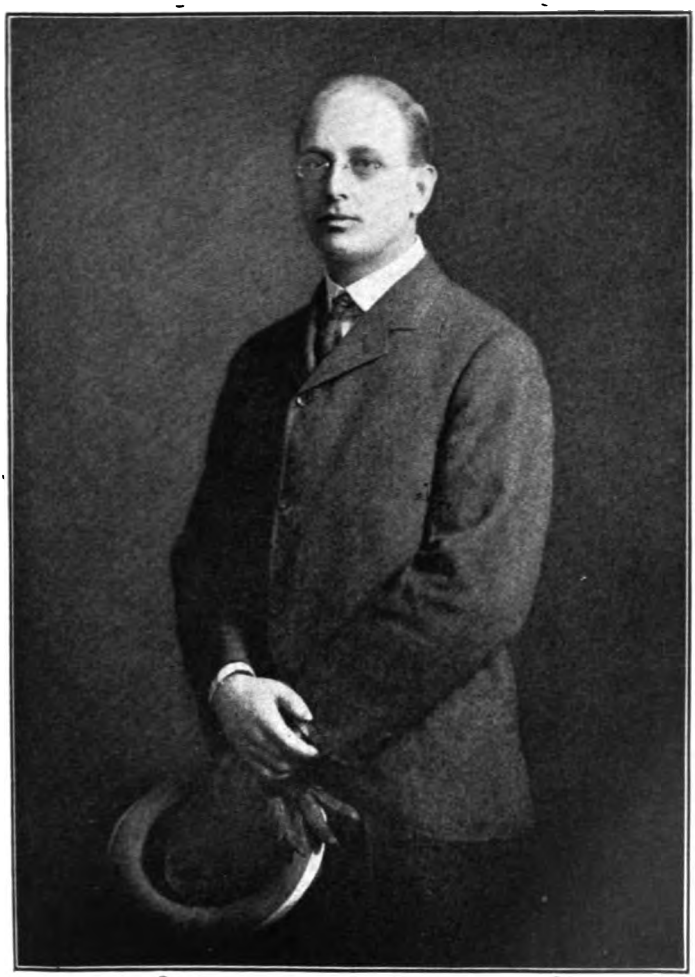

George Blumer.

DIRECTOR OF THE BENDER HYGIENIC LABORATORY, 1896-1903

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With A. VANDER VEER, M. D.

41—Resumé of the Subject of Actinomycosis with Report of a Case of Abdominal Actinomycosis, ALBANY MEDICAL ANNALS, January, 1903.

HARRY W. CAREY, M. D.

42—Report of Two Testicular Teratomata with a Review of the Recent Literature, *Johns Hopkins Hospital Bulletin*, November, 1902.

43—The Presence of the Shiga Variety of Dysentery Bacilli in an Extensive Epidemic of Dysentery, *Journal of Medical Research*, March, 1903.

ARTHUR T. LAIRD, M. D.

44—Recent Studies Regarding the Morphology of the Diphtheria Bacillus, ALBANY MEDICAL ANNALS, 1903, xxiv, 251.

With CHARLES E. DAVIS, M. D.

45—A Case of Diphtheria, ALBANY MEDICAL ANNALS, 1901, xxii, 499

HARRIS MOAK, M. D.

46—On the Occurrence of Carcinoma and Tuberculosis in the Same Organ or Tissue, *Journal of Medical Research*, 1902, viii, 128.

THOMAS G. DICKSON, M. D.

47—Concerning the Nature of the Small Cysts Frequently Found in the Peritoneum Covering the Fallopian Tubes, *American Journal of Obstetrics*, 1903, xlviii, no. 1.

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Reprinted from ALBANY MEDICAL ANNALS, November, 1904.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1904.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1904.

Organization—The equipment of the laboratory and the organization of its work by my predecessor, Dr. George Blumer, were such that upon September 1st, 1903, I was able to enter upon my duties under the most favorable circumstances. The staff of the laboratory was immediately completed by the appointment, as assistants, of Edwin MacDonald Stanton (Iowa State College, B. S., 1898; University of Pennsylvania, M. D., 1903) and of Charles Knickerbacker Winne, Jr., (Johns Hopkins University, A. B., 1897; M. D., 1901). Early in the year it was evident that the clerical work had increased to such an extent that the full time of a stenographer would be required; and with your approval this service has been provided. It was also found that much valuable time was consumed by the members of the staff in semi-technical work which could be done as well at a moderate cost by a non-medical assistant. By arrangement with the faculty of the Albany Medical College the additional salary was guaranteed and the appointment was made. Both of these changes have aided greatly in the routine work of the laboratory.

Mr. Leonard M. Wachter was reappointed for the year 1904-'05 as assistant chemist and bacteriologist, in charge of the Albany filtration plant.

The Work of the Laboratory—This may be conveniently divided into routine examinations, under-graduate teaching, instruction to special students and original investigations.

The nature of the routine work of the laboratory is shown in the accompanying table which gives the source of the material and the number and character of the examinations. This table does not include the bacteriological studies carried out in connection with the autopsy work, the tests made for the milk committee

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of the Albany County Medical Society, or the examinations of "winter-killed" deer, made during the past winter for the New York State Forestry, Fish and Game Commission. Mr. Wachter's report of his chemical and bacteriological examinations, made at the filtration plant, have been included in his annual statement to the Water Bureau of the City of Albany and do not appear in this report.

TABULATION OF THE ROUTINE EXAMINATIONS MADE AT THE BENDER LABORATORY FROM SEPTEMBER 1, 1903, TO AUGUST 31, 1904

	State Dep't. of Health	City Board of Health	Albany Hospital	St. Peter's Hospital	Child's Hosp. and St. Margaret's House	Albany Orphan Asylum	Alms House	Coroner's Physicians	Physicians	
Sputum	272	35			2				32	341
Widals	106	10	77	5	2	2			34	226
Throat cultures	729	713				83			142	1667
Water, milk and ice	407		3		1	1			46	458
Miscellaneous examinations	5		52	2	2				69	130
Surgical specimens			939	19	3				42	1003
Autopsies			42	1	10	6	8	31	25	123
	1519	758	1113	27	20	92	8	31	390	3958

The examination of surgical specimens has been greatly facilitated by the general adoption of Wright's frozen section method which ensures the surgeons of an early report and also lessens the daily labor in the laboratory. The custom adopted by the Albany Hospital, at our suggestion, of forwarding with each specimen a printed form upon which is entered the important data concerning the tissue to be examined allows a more intelligent examination, and also enables us to keep more complete laboratory records. As will be seen by the accompanying table, the examination of

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material from the surgical service of the Albany Hospital constitute a large share of our routine work. For the performance of this work the hospital contributes neither service nor money. It has occurred to me that hospital and laboratory alike would be greatly benefited by the appointment of a pathological house officer whose duty it would be to assist in that part of the hospital work carried on in the laboratory. In return for this service the hospital should furnish him with room and board. This assistant should be a graduate in medicine and preferably one with post-graduate hospital training. Such an arrangement has been practiced for years at the Boston City Hospital which indeed has two pathological internes and in that institution has proved most satisfactory. I believe it might profitably be adopted by the Albany Hospital and respectfully suggest it to your board.

I wish also to call your attention to the great increase in the amount of work done for the State Department of Health. This increase of work has not been accompanied by an increase of appropriation; and the labor is out of all proportion to the compensation. I think an effort should be made to secure a larger appropriation. The rapid development of this work is shown in the following table, which is based on examinations made from September 1, to August 31st.

	Throat cultures	Sputum	Widal reactions	Water, milk, ice and sewage
1901-'02	222	33	11	90
1902-'03	807	71	50	184
1903-'04	729	256	123	412

The laboratory courses given during the past year (term of seven and a half months) to undergraduates of the Albany Medical School are as follows:

Pathology and bacteriology—Drs. Pearce, Stanton and Winne, eight and a half hours a week.

Normal histology—Drs. Stanton and Winne, six hours a week.

Clinical microscopy—Dr. Laird, two and a half hours a week.

Surgical pathology—Drs. Elting and Carey, two and a half hours a week.

Histology and pathology, in connection with the course in obstetrics—Dr. Lipes, two and a half hours a week.

Anatomy of the nervous system—Dr. Becker, one hour a week.

For the year 1904-'05 several changes have been made in these courses. The need of more detailed instruction in the methods

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of clinical microscopy has led to the division of this class into two sections and the appointment of another assistant, Dr. E. F. Sibley. The course in the anatomy and pathology of the nervous system has been placed under the direction of Dr. Stanton who will be assisted in this work, as well as in the course in histology, by Dr. Donald Boyd.

In connection with the course in pathology the most serious need is some arrangement by which post-mortem examinations may be made before the entire class. At present, this instruction can be given only to small sections at irregular intervals. It would appear possible, by combined action of the Albany Hospital, the faculty of the Medical School and the trustees of the laboratory, to arrange for proper facilities at the Albany Hospital. I respectfully suggest to the trustees the necessity of immediate action upon this question.

Of those who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are Dr. Ellice McDonald, of Philadelphia; Mr. Leon K. Baldauf, of the Johns Hopkins Medical School; Dr. J. F. Rooney, Dr. E. F. Sibley and Dr. Donald Boyd, of Albany; Mr. Joseph L. Donhauser, Mr. Erastus Corning, Mr. C. W. H. Hacker and Mr. T. A. Hull, of the Albany Medical School; Mr. Jerome Meyers, of Dartmouth College; and Mr. W. E. Wright, of Liberty, N. Y. These gentlemen have assisted in the routine work of the laboratory, pursued special lines of study, or engaged in research work. To Dr. Ellice McDonald, we are especially grateful for valuable assistance during the first half of the year.

For the year 1904-'05 Dr. E. F. Sibley has agreed to serve as voluntary assistant in all laboratory work.

Original investigations in various lines of work have been carried out during the year. The expense of the experimental investigations has been defrayed by a grant from the Rockefeller Institute for Medical Research; a similar grant has been obtained for the year 1904-'05. The following papers have been published or are now in press:

1. Pearce, R. M., Concerning the Specificity of the Somatogenic Cytotoxins.
   (Conducted under a grant from the Rockefeller Institute for Medical Research).
   Journal of Medical Research, 1904, xxi, 1; also Albany Medical Annals, 1904, xxv, 576.

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2. PEARCE, R. M., The Experimental Production of Liver Necroses by Haemagglutinins, (*in press*).
(Conducted under a grant from the Rockefeller Institute for Medical Research).

3. PEARCE, R. M., and WINNE, C. K., Jr., Concerning Haemagglutinins of Bacterial Origin and their Relation to Hyaline Thrombi and Liver Necroses, (*in press*).
(Conducted under a grant from the Rockefeller Institute for Medical Research).

4. PEARCE, R. M., The Islands of Langerhans in Congenital Syphilitic Pancreatitis.
American Medicine, 1903; vi, 1020; also, ALBANY MEDICAL ANNALS, 1904, xxv. 88.

5. PEARCE, R. M., The Pathology of Diabetes.
ALBANY MEDICAL ANNALS, 1904, xxv, 329.

6. PEARCE, R. M., Experimental Pancreatitis Considered in its Relation to Acute Lesions of the Pancreas in Man.
American Medicine, 1904, vii, 853; also ALBANY MEDICAL ANNALS, 1904, xxv, 389.

7. PEARCE, R. M., Cancer of the Pancreas and Glycosuria; A Histological Study of the Islands of Langerhans, (*in press*).

8. McDONALD, E., Complications and Degenerations of Uterine Fibromyomata.
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In pursuance of a plan already submitted to you it is my intention to prepare for general distribution a volume which will contain the above papers. This volume will be known as "Studies from the Bender Laboratory," and with your financial support, I hope to make it an annual publication.

Improvements and Repairs—These have not been extensive. The need, however, of more space for the general work of the laboratory led me to convert the large room on the first floor, formerly occupied by the janitor, into an office for the stenographer and the proper storing of the laboratory records. The janitor has been given the room on the third floor, formerly a cloak room for the use of students. The latter have been provided for by placing hooks in the large hall off the class room of this floor. Three small private rooms intended for the use of persons conducting special researches have been procured by partitions isolating the unused portion of the large class room on the third floor. These assure more or less privacy and add to the desk space available for special work. Other improvements include an additional work table in the director's room, a work bench in the basement with vise and tools for the janitor's department, important changes in the arrangement of the animal room and additional shelving in various parts of the building. During the past summer all the floors have been filled and oiled, the wood work of halls and lecture room varnished, the walls of halls and office painted, and various repairs to the windows made. To prevent a repetition of the disastrous flooding of the basement which occurred during the freshets of last spring, the ground at the rear of the building has been raised and sodded and the walls and cover of the cellarway repaired. The appearance of the front of the building has been improved by cleaning the brick work and repointing the stone work and steps.

Gifts—A portrait of Mr. Matthew W. Bender, presented by Dr. George E. Gorham, has been placed in the lower hall; a series of fifty-one portraits, the gift of Dr. George Blumer, representing prominent workers in scientific medicine, in the large class room of the third floor; and a portrait of Dr. George Blumer, in the Director's room.

RICHARD M. PEARCE.

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Reprinted from ALBANY MEDICAL ANNALS, August, 1904.

CONCERNING THE SPECIFICITY OF THE SOMATOGENIC CYTOTOXINS.*

Presented at the Fourth Annual Meeting of the American Association of Pathologists and Bacteriologists, held at New York, April 1st and 2nd, 1904.

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CONTENTS

Introduction—Methods—Observation of immunized animals—On the action of anti-sera obtained by the injection of (*a*) red blood cells, (*b*) liver, pancreas, adrenal and kidney containing blood, (*c*) the same organs free of blood, (*d*) blood serum, (*e*) urine, and (*f*) bile—Controls with normal serum—Relative toxicity of the various sera—Summary and Conclusions—References.

INTRODUCTION

This study was undertaken with the object of demonstrating, by a comparative study of the somatogenic cytotoxins, that the action of any given cytotoxin depends on the chemical (receptor) organization of the cell and not upon morphological characteristics; that an artificial anti-serum may have a definite toxic action on several types of cells of widely differing morphology but presumably having in part at least common receptors; that specificity in the sense of morphological affinity is of secondary importance and in the case of some sera may not exist; that many of the results supposed to be due to the specific action of one cytotoxin

* This study has been conducted under a grant from the Rockefeller Institute for Medical Research.

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are due rather to other cytotoxins adventitiously elaborated as the result of improper methods of immunization.

My attention was first attracted to these various phases of cytotoxic activity by some observations made in the course of an experimental investigation of nephrotoxins.* I found that by the usual method of immunization, that is, the injection of the kidney with its contained blood, a serum strongly haemagglutinative and haemolytic was produced and that the haemoglobinuria resulting from the injection of this serum entirely obscured any nephrolytic action it might possess. The haemagglutinative element of the serum also caused the agglutination of the red blood corpuscles; the thrombi thus formed occluding the vessels of the liver with resulting focal necroses of that organ. It was therefore evident that many of the results previously reported as due to a specific nephrotoxin or hepatotoxin were due to haemagglutinins or haemolysins forming in animals improperly immunized. To obviate this difficulty blood-free kidney was used in the immunization with the surprising result that although the serum thus obtained was powerfully nephrotoxic, it was also, in a moderate degree, haemagglutinative and haemolytic. It did not however cause haemoglobinuria. Moreover hepatotoxin, so-called, prepared in like manner possessed similar characteristics but exerted no special action upon the liver.

At this time an extended investigation of the literature indicated that immunization with "washed" or blood free organs had in no instance been practiced. It was evident therefore that a study of cytotoxins by this method of immunization might yield results differing widely from those of previous investigations and possibly of fundamental importance in connection with the question of the specificity of these substances. Before taking up the detailed discussion of this work, it may be well to summarize the more important communications upon the question of specificity.

In the vast amount of literature which has accumulated the

*Pearce. An Experimental Study of Nephrotoxins, *Univ. of Penna. Med. Bulletin*, 1903, xvi, 217.

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predominating feature is the effort to demonstrate a morphological affinity. This is especially evident in the early work which neglects to a great extent the question of chemical (or receptorial) structure. Due consideration has not been given to the very clear and definite statements of Ehrlich and Morgenroth concerning specificity. v. Dungern and Mexter produced anti-sera for ciliated epithelium and testicular cells and found them to be also haemolytic. On account of these results they denied a strict specificity to the cytotoxins. Metchnikoff and Metalnikoff, on the other hand, believing in this specificity, endeavored to explain the double action on the supposition that sufficient red blood corpuscles were injected with the epithelial cells to produce an haemolysin.

Of wider interest is the production of haemolysins by injecting body fluids entirely free of red corpuscles. v. Dungern, Besredka, Tschistovitsch, Müller and Morgenroth by injecting blood serum, and Shattenfroh, Buffer and Crendiropoulo by injecting urine have obtained such. v. Dungern produced an haemolysin also by injecting cow's milk, and recently Portis has obtained a like result by injecting the "colloid matter" of the thyroid. These observations, at first glance opposed to the theory of specificity if considered from the point of view of morphology, are explained by Morgenroth by the presence of free receptors in the blood and urine. These free receptors, as first announced by Ehrlich, appear in these fluids, especially the blood, as the result of the cell changes accompanying normal metabolism. Thus it is possible for receptors of all cells of the body to be present in the blood serum. Naturally, immunization with fluids containing these receptors would result in the formation of specific anti-bodies. Morgenroth therefore draws the conclusion that specificity is a matter not of cells but of receptors, whence a given cell may be in chemical conformity with cells of a different organ or perhaps animal. Recent investigations of anti-thyroid serum (Yates, MacCallum, and Portis) and of anti-adrenal serum (Abbott, Yates) indicate that these

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have little or no specific action. Unwashed adrenal serum, however, Abbott found to be possessed of a definite haemolytic power; Portis found the same to be true of washed thyroid serum.

In order to study this much debated question of specificity in a somewhat comprehensive manner a comparative investigation of several cytotoxins, as outlined in the introductory summary, was undertaken.

METHODS

The animals selected for this study were the dog and the rabbit; the latter being immunized with the cells and fluids of the former. The method of immunization adopted was that followed in the work on nephrotoxins. All injections were made into the peritoneal cavity at intervals of a week or ten days, the animal being bled a like period after the third, fourth or fifth injection. Preliminary bleedings were made from the jugular veins; the final bleeding from the carotid arteries. The serum thus obtained was injected into the saphenous, occasionally the femoral vein of the dog. In determining the specific effect of these various sera, systematic examinations of the urine and detailed gross and histological studies of the several organs have been made; their action upon red blood corpuscles has been determined *in vitro*. Attempts were also made to determine by the test-tube method the action of the various sera upon emulsions of the several types of parenchymatous cells; but the results were so confusing and contradictory that this method was early discarded in favor of intravenous injection. This method, analogous to pharmacological methods, of testing the action of a serum by its effect on the living cells is, I believe, the only method free of error. Moreover, it is by this method alone that the cytotoxins may be utilized to explain various pathological processes, for while tests *in vitro* may establish the theoretical principles of this method of investigation, substantial progress depends on the experimental application to the living cell in its normal environment.

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Some information concerning what may be called the more general action of a serum has been determined by observing fluctuations in body weight; and of the relative lethal action, by a comparative study of dosage.

The histological methods include hardening in Zenkers, Müller's and Fleming's solutions; imbedding in celloidin and paraffin; and staining by haemotaxylin and eosin, methylen blue and eosin, Mallory's connective tissue stain and saffranin. The various fresh methods have been utilized in the study of fatty and pigmentary changes.

OBSERVATIONS OF IMMUNIZED ANIMALS

Contrary to general opinion the rabbit may readily be treated with various animal cells and fluids if due attention is paid to cleanliness and to the condition of the animal as shown by fluctuations in body weight. In this series the only deaths occurred among rabbits receiving bile and unwashed liver. Fifty per cent. of the animals treated with these substances succumbed before the third injection. This result is apparently due to the toxicity of bile, for no difficulty was encountered in animals receiving washed liver, blood corpuscles or blood serum. The kidneys of animals dying within a few days after the injection of bile exhibit a well marked degeneration of the convoluted tubules with deposition of a yellowish pigment.

Necrosis and suppuration of the subcutaneous tissues may occasionally occur after the injection of organ emulsions; while encapsulated masses of the injected material in the peritoneal cavity are not infrequent. In one instance after injection of pancreas emulsions fat necroses of the mesenteric, perirenal and pelvic fat were observed.

The changes in the urine are but slight; a heightening of color may occur not uncommonly after injections of blood and adrenal; slight traces of albumen are infrequently found; glycosuria, transitory and of slight degree usually follows the injection of adrenal.

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The several organs of these various animals with the exception of those receiving bile, exhibited no histological changes of any moment.

ACTION OF SERUM RESULTING FROM THE INJECTION OF ERYTHROCYTES

While the action of haemolytic sera *in vitro* is well known, little attention has been paid to the changes resulting from its injection into the living animal. Kraus and Fukuhara only, as far as I am aware, have described the histological changes. As such observations are essential, as controls to the experiments to follow, I have made a careful study of this phase of the subject. Rabbits were immunized with defibrinated and washed blood respectively, receiving three to five doses of five centimetres each. Whether defibrinated blood or washed corpuscles are used appears to make no difference in the potency of the serum. Seventeen dogs have received this serum, intravenously, in doses varying from 1 :3000 to 1 :450.* The effect varied with the dosage. In large amounts (1 :600 to 1 :400) death usually occurs in from three to fifteen hours. Post-mortem examination of dogs poisoned in this way show the blood to be laked and soft gelatinous clots to be present in the heart and large vessels. The internal organs especially the liver, are intensely congested; the serous cavities may contain a small amount of blood tinged fluid. If the bladder contains urine it is dark claret colored, rich in albumen with a sediment composed of casts, coalesced masses of altered haemoglobin and granular and fatty renal cells. Histological examination reveals agglutinated red blood corpuscles in the various organs; the vessels of the spleen and liver are intensely congested, the cells of the latter often being compressed and disorganized; beginning necrosis of liver cells is not infrequent. The kidney tubules present a wide-spread fatty meta-

* This method of indicating the dose refers to the relation between the amount of serum injected and the weight of the animal. Thus 1:525 indicates that a dog weighing 6300 grammes received 12 c. c. of serum or 1 c. c. to 525 grammes of body weight.

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morphosis; their lumina contain altered haemoglobin in the form of casts or irregular granular material; the tissue spaces are oedematous and an accumulation of coagulated serum may be seen in the glomerular spaces.

The smaller doses of 1 :1000 to 1 :700 are usually not fatal; but the dogs develop within eighteen to twenty-four hours a haemoglobinuria which persists for three to five days. After the disappearance of the haemoglobin the urine is still high colored and deeply stained with bile. A yellow jaundiced condition of the conjunctivae is a constant symptom. The albuminuria which accompanies the acute condition rapidly diminishes as the urine becomes clear of blood pigment although it may be detected by the heat test for many days; in one animal persisting for three weeks. The urinary sediment contains the products of the destruction of red blood corpuscles and usually many renal cells. Beginning with the second or third day a few casts of the finely granular type are found, but not invariably. Hyaline liver necroses* due to agglutinated red blood corpuscle thrombi are constantly present in these animals. Equally constant is a fatty degeneration of the kidney, which is most marked in the tubules of the medullary rays. Hemorrhages into the adrenal occurred in two of the seventeen animals. They were also found occasionally in the lung.

With doses as low as 1 :1200 to 1 :3000 haemoglobinuria does not always result, but the urine is bile stained and contains albumen. Changes similar to those described above but less marked may occur in the liver and kidney.

The attempts to produce haemolytic sera with small amounts of blood have been of great interest. These were undertaken for the purpose of controlling sera prepared by injecting organs (adrenal) which contain an amount of blood so small that it has heretofore been considered negligible. A series of rabbits receiving 0.1 cubic centimetre of defibrinated blood yielded, after the second injection, a serum which was moderately agglutinative and haemolytic *in*

* This condition has been the subject of especial investigation and will be considered in detail in another communication.

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vitro; after five injections the serum was immediately and powerfully agglutinative and haemolytic. This serum injected into dogs in doses of 1 :550 to 1 :345 causes haemoglobinuria, multiple liver necroses, fatty degeneration of the kidney and other changes, including adrenal haemorrhages, similar to those produced by sera prepared from larger amounts of blood. One dog, receiving a dose of 1 :350, died in four hours with evidence of extensive thrombosis due to agglutinated red blood corpuscles.

SERUM FROM UNWASHED ORGANS (KIDNEY, LIVER, PANCREAS AND ADRENAL)

In this series the serum was prepared in the usual manner by injecting emulsions of the unwashed organ, that is, with the normal post-mortem blood content. Four to twelve grammes were used at each injection of kidney, liver and pancreas; while animals immunized against adrenal cells received a pair of the organs at each injection. The experience of Yates in the production of adrenal serum indicates that a larger amount of adrenal tissue has no appreciable effect on the character of the serum.

All these sera, naturally, contain haemagglutinin and haemolysin. The liver, kidney and adrenal sera injected into the dog in doses of 1 :900 to 1 :300 produce similar changes which, moreover, cannot be distinguished from those due to a pure haemolytic serum. Haemoglobinuria, liver necroses, fatty degeneration of the kidney and deposition of blood pigment in spleen and lymph nodes are constant. Only in the case of the kidney serum was a dual action evident. Here, the persistence of albumen and a larger number of casts (granular, epithelial and fatty) after the disappearance of the haemoglobinuria indicated the action of the specific nephrotoxic constituent. This serum saturated with washed red blood corpuscles at zero temperature lost all but a trace of its haemolytic power but was still powerfully nephrotoxic.

No changes occurred in the liver or adrenal which could be ascribed to their supposedly specific sera. The kidney serum in one

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instance produced focal hemorrhages in the adrenal; the adrenal serum similar lesions in the lung.

The pancreas serum in doses of 1 :800 to 1 :390 did not produce haemoglobinuria but a persistent albuminuria with fatty degeneration of the kidney. The strongest dose given (1 :390) caused also well marked focal necroses of the liver with evidence of red blood cell thrombosis. No change in the pancreas cells could be demonstrated.

Of these four sera that prepared from adrenal appears to be the most toxic, causing death in less than twenty-four hours in dose of 1 :400.

It will be seen from this summary that these sera, with the possible exception of nephrotoxin, produce lesions which differ in no way from those due to a serum prepared from erythrocytes and that they may all readily be explained by the action of haemagglutinin or haemolysin.

SERA PREPARED FROM WASHED ORGANS (KIDNEY, LIVER, PANCREAS AND ADRENAL)

In this series the blood, lymph and the various secretions with their free receptors were removed from the organs by prolonged washing with warm, sterile salt solution. After this procedure it was assumed that only the cells with their fixed receptors remained. The kidney was readily washed through its arteries; the adrenal, pancreas and liver at one time through the abdominal aorta; the clearing of the liver vessels was augumented by washing also through the portal vein. The success of this procedure was tested by immediate examination of the respective organ emulsions and later by examination of hardened sections of the organs. Kidney, adrenal and pancreas, absolutely blood free, were readily obtained; a very few red cells (one or two in three or four fields) were always found in the liver emulsions, despite the most thorough washings with fifteen to twenty litres of salt solution. These cells, however, appear to have had little influence upon the character of the serum produced.

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All sera resulting from the injection of these blood free emulsions have the power of agglutinating and haemolysing red blood corpuscles *in vitro*. The agglutination in all instances is immediate and powerful. The haemolytic activity of the adrenal serum is almost equal to that of serum prepared from red blood corpuscles; liver, pancreas and kidney sera are less powerful, their relative strength being in the order named. None of these sera on the other hand are sufficiently powerful to produce haemoglobinuria when injected into the circulation of the dog. My experience is different from that of Portis, who has recently described a serum prepared from washed thyroid, which is haemolytic *in vitro* and in animals produces haemoglobinuria.

The only one of these sera which has a definite action in the sense of morphological specificity is nephrotoxin. The action of this cytotoxin I have recently described in detail, and only a general summary is now necessary. Doses of 1:1600 to 1:500 produce severe albuminuria and cast excretion. The casts are finely granular, and less frequently fatty, epithelial and hyaline; granular and fatty renal cells are usually abundant. The albumen gradually diminishes in amount, but may persist in faint traces for two weeks or more; the casts usually disappear within twelve to fifteen days. The kidney is swollen and oedematous with slightly adherent capsule. On section the cortex is oedematous and pale yellow in color with occasionally a few punctate haemorrhages; the glomeruli are distinct but pale. Histologically the cells of the convoluted tubules are found to be swollen and granular; the cells of the tubules in the medullary rays are vacuolated and osmic acid preparations reveal extensive fatty metamorphosis; the tubules especially those of the pyramids contain much granular material and many casts. Exudation into the glomerular space and hyaline thrombosis with degeneration of the glomerular tuft may occur. With the exception of the liver, which in some animals exhibited extensive granular degeneration no other organs appear to be affected by this serum.

The action of the so-called hepatotoxin is variable. In doses of

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1 :1000 to 1 :525 its chief action is to cause a more or less extensive fatty metamorphosis of the kidney. This may or may not be accompanied by albuminuria; in two experiments the albuminuria was equal to that resulting from the administration of nephrotoxin and abundant excretion of casts was present. That definite changes are produced in the liver by this serum is not easily determined. The only change observed was an increased granulation of the liver cells with occasionally slight fatty transformation. This appearance however does not differ from that frequently seen in the liver of apparently normal dogs and is quite constant after the administration of other anti-sera, especially adrenal serum. Focal necroses of the liver due to this serum I have seen in but one instance. These were few in number and followed the administration of a powerful dose (1 :266) of a strongly haemagglutinative serum. As agglutinated masses of red blood corpuscles could be seen in the vessels of the necrotic areas, I consider this action to be due to the agglutinin present and not to a hepatotoxic constitutent of the serum. The necroses described by Delezenne and others working with serum prepared from the unwashed organ may, I believe, be explained in like manner. The changes in the urine described by Delezenne I have not seen.

Adrenal serum in doses of 1 :700 to 1 :550 produces no lesion of the adrenal gland; but well marked granular and fatty transformation of liver and kidney. One animal, killed forty-eight hours after a dose of 1 :556, presented multiple minute haemorrhages of the lungs and liver with free haemorrhages into the glomerular spaces of the kidney. A peculiar phenomenon observed in all animals receiving adrenal serum was an immediate blanching of the mucous membranes with cardiac and respiratory disturbance. This condition, which lasted fifteen to twenty minutes and necessitated the employment of artificial respiration, was not observed in animals receiving other cytotoxic sera. Unfortunately a kymographic study of this condition was not made.

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Washed pancreas serum produces in doses as high as 1:620 no recognizable changes in the pancreas and but moderate granular and fatty metamorphosis of the liver and kidney. The transitory glycosuria described by Surmont and by Carnot and Garnier I have not seen. Their injections were made, however, directly into the pancreas; the glycosuria therefore may have been the result of trauma and analogous to that observed by Flexner and Pearce to follow various injuries to the pancreas.

SERA PREPARED BY INJECTING BLOOD SERUM, BILE AND URINE

As has been stated above, several investigators have produced haemolytic sera by immunizing animals with blood serum, urine and other fluids free of red blood corpuscles. This result Morgenroth explains is due to the presence of free receptors normally constitutents of the body fluids. In order to determine if sera thus prepared contain cytotoxins for cells other than red blood corpuscles; also to control other experiments of this series, I have injected rabbits three to five times with the blood serum, bile and urine of the dog in doses of five to ten cubic centimetres.

All three sera thus prepared are strongly haemagglutinative. The serum produced by injecting urine is powerfully haemolytic, that by injecting serum, moderately haemolytic, while the "anti-bile" serum has no haemolytic power whatever. This peculiarity of "anti-bile" serum has been observed recently by Ruffer and Crendiropoulo, and is apparently to be explained by the production of anti-haemolysin, the bile being naturally haemolytic.

"Anti-bile" serum in doses of 1:620 and 1:700 causes fatty degeneration of the kidney and focal necroses of the liver. These latter are accompanied by agglutinative red-blood corpuscle thrombosis and apparently due to a mechanical disturbance of the liver circulation. No changes are found in other organs.

The serum of rabbits receiving dog's serum injected in doses of 1:1000 to 1:390 causes extensive fatty degeneration of the kidney with sometimes slight traces of albumen in the urine.

The serum of rabbits receiving dog's urine produces in the dog

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a distinct congestion of the liver; otherwise no appreciable changes of either tissues or excretions follow doses as high as 1 :674.

CONTROLS WITH NORMAL RABBIT'S SERUM

Normal rabbit's serum injected in doses of 1 :1320, 1 :900, 1 :600, 1 :500 and 1 :300 was without influence on the urine or histological structure of the various organs examined (kidney, liver, pancreas and adrenal).

RELATIVE TOXICITY OF THE VARIOUS SERA

An attempt has been made in addition to the above described methods of study to gain some idea of the relative toxicity of the various sera by a comparison of the changes in body weight and of the varying periods of time elapsing before fatal termination. Little information has been obtained by the study of changes in weight, for while a loss of weight is more or less constant, there is little variation according to the kind of serum injected, except that an appreciably greater loss of weight occurs in animals receiving sera which produce albuminuria (nephrotoxin) and haemoglobinuria (haemolysins produced by defibrinated blood and unwashed organs).

Death followed only after the use of sera prepared from red blood corpuscles and from blood containing organs. With the exception of the powerful nephrotoxin, prepared from washed kidney cortex, described in a previous communication,* death has never resulted from the injection of sera prepared from washed parenchymatous cells or from blood-free body fluids. There is apparently considerable difference in the toxicity of the haemolysin produced by the injection of red corpuscles and those produced by washed parenchymatous cells; washed adrenal serum, for example, the haemolytic power of which *in vitro* is almost as great as that of true haemolysin has never caused death. On the other hand, it is of interest that the lethal power of a serum pro-

* *Loc cit.*, page 228.

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duced by blood injected in 0.1 cubic centimetre doses is almost as great as that following the injection of five cubic centimetre doses The former has caused death in four hours, in dose of 1:350; the latter in three hours, in dose of 1:450. With these sera may be compared the unwashed adrenal serum which caused death in less than twenty-four hours in dose of 1:400. These results indicate that as a general rule the power of a serum is not increased by large immunizing doses.

SUMMARY AND CONCLUSIONS

From these experiments it is evident that the cells of the various organs of the body while differing in morphology and function have certain receptor characteristics in common and that one type of cell may therefore produce anti-bodies affecting several cells of differing morphology but with like receptor groups. This is shown by the sera prepared from washed liver, kidney, pancreas and adrenal, all of which agglutinate and haemolyse red blood corpuscles, and may cause degenerative changes also in the liver and kidney. Some of these cytotoxic sera have no effect upon organs for which they are supposed to have a morphological affinity, but exert a powerful lytic influence upon other cells. Aside from nephrotoxin, which has a distinct injurious action upon renal epithelium the various cytotoxins studied have no specific action in the morphological sense. The action of the kidney serum itself cannot be said to be specific, for in addition to the nephrotoxic element another constitutent (haemolysin) is present. The action of this serum might perhaps be described as "special." Pancreas and adrenal serum on the other hand are devoid even of special action, while the lesions of so-called hepatotoxin are doubtful and may be produced by other sera. The striking characteristic of adrenal serum is its powerful haemolysin.

The presence of free receptors in the various body fluids is shown by the appearance of anti-bodies in the serum of animals

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receiving serum, bile and urine; the diverse character of these receptors by the variety of cytotoxins thus formed. These observations offer strong support of the view that specificity is a function of receptors and not of cells.

A comparison of the results obtained by sera prepared from washed organs with those of sera prepared from blood and blood containing organs indicates that many of the positive results described as specific and characteristic of the action of certain cytotoxins are due rather to haemagglutinin and haemolysin adventitiously formed as the result of impure methods of immunization.

In connection with the activity of haemolysin it is also necessary to differentiate sharply between the primary specific action upon the red blood cells and the secondary action upon other cells, as those of the kidney, due to the toxic effect of haemoglobin derivatives and possibly other substances set free by the destruction of the red blood cells.

Another phase of the question, heretofore entirely disregarded, is the part played by haemagglutinin. This substance was present in all the sera studied, and in some, when sufficiently powerful, caused the formation of red blood corpuscle thrombi and a resulting mechanical disturbance of the circulation leading to degeneration, necrosis and haemorrhage. This action is best illustrated by "anti-bile" serum which is without haemolytic power, but through its powerful agglutinin causes the formation of red blood corpuscle thrombi and thus the production of widespread liver necrosis. Such lesions have heretofore been confounded with the action of the cytolytic constituent of a serum, and have been considered specific while they are in truth due to the much simpler agglutinating body.

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Reprinted from ALBANY MEDICAL ANNALS, October, 1904.

THE EXPERIMENTAL PRODUCTION OF LIVER NECROSES BY THE INTRAVENOUS INJECTION OF HAEMAGGLUTININS.*

Presented before the American Association of Pathologists and Bacteriologists at the fourth annual meeting held in New York, April 1 and 2, 1904.

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Introduction—This investigation was undertaken with the object of demonstrating experimentally that red blood corpuscles through the agency of agglutinins become fused together and form thrombi which occluding the vessels of the liver may lead to hyaline necrosis of liver cells. That these lesions might thus be produced, was indicated by observations made during a study of various cytolytic sera. In the course of an experimental study of nephrotoxins,[1] it was noted that focal necrotic lesions of the liver with associated hyaline thrombi frequently followed the intravenous injection of sera possessing considerable hæmagglutinative power, but did not follow the injection of sera devoid of this characteristic. Flexner's[2] communication concerning agglutinated red blood corpuscle thrombi, which had appeared but a short time before, suggested the possibility of these hyaline thrombi being composed of red blood corpuscles. A careful study of the lesions proved this to be the case, and a series of experiments was therefore at once begun for the purpose of establishing definitely the power of agglutinin to produce red cell thrombi and also to establish a relation between the thrombi and the necrotic lesions. Later, my interest in the subject was stimulated by the appearance of Boxmeyer's[3] work on the liver necrosis of hog cholera. Boxmeyer found that while one type

* This investigation was conducted under a grant from the Rockefeller Institute for Medical Research.

[1] PEARCE. An Experimental Study of the Nephrotoxins, *University of Penn. Med. Bull.* 1903, xvi, 217.

[2] FLEXNER. *University of Penn. Med. Bull.*, 1902, xv, 324.

[3] BOXMEYER. *Journal of Medical Research*, 1903, ix, 146.

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of lesion was due to a plugging of the capillaries by endothelial cells, aided probably also by a direct action of the toxins upon the liver cells, another type could be explained only by the occlusion of capillaries by fused masses of red blood corpuscles (hyaline thrombi). Although he believed the fusion of these cells to be due to an agglutinin, he made no tests to demonstrate its presence.

As far as I am aware no efforts have heretofore been made to demonstrate experimentally a relation between agglutinins and liver necroses. Focal necrotic lesions of the liver following the injection of cytotoxic sera have been described by Delezenne,[4] Kraus[5] and Fukuhara,[6] but in no instance has it been suggested that agglutinins were concerned in their production.

Methods—Hæmagglutinative sera have been prepared by injecting the rabbit with various organs and fluids of the dog. As the investigation was carried on simultaneously with another which had for its object the determination of the relative specificity of the somatogenic cytotoxins,[7] it has been possible to work with a large number of artificial sera. These include sera prepared by injecting defibrinated blood, washed blood corpuscles, blood serum, bile, urine and washed and unwashed liver, pancreas, kidney and adrenal. All these sera possess the power of agglutinating the red blood corpuscles of the dog in vitro; all, however, as will be seen are not sufficiently powerful to cause red blood corpuscle thrombi in the living animal. The sera was injected under ether anæsthesia, into the saphenous vein of the dog, and after varying periods of time the animals were killed by chloroform. The histological methods of examination include hardening in Zenker's, Müller's and Fleming's solutions; imbedding in celloidin and paraffin; and staining by hæmatoxylin and eosin, methylen blue and eosin, Mallory's connective tissue stain, Weigert's fibrin stain and safranin.

General Summary of Results—Liver necroses were readily produced by sera obtained by injecting bile, blood and blood containing organs; they did not occur after the use of sera

[4] Delezenne. *C. R. de l' Acad. des Sciences*, 1900, cxxxi, 437, cited by Sach, *Biochem., Centralb.*, 1903, i, 616.
[5] Kraus. *Verhandl. d. Deutsch. Path. Gesellsch.*, 1902, v, 58.
[6] Fukuhara. *Ziegler's Beiträge*, 1904, xxxv, 434.
[7] Pearce. Concerning the Specificity of the Somatogenic Cytotoxins, *Jour. of Med. Research*, 1904, xii, 1.

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prepared by injecting urine, serum and washed organs, except in one instance in which an exceedingly high dose of washed liver serum was administered. The power of these several sera to produce conglutinative thrombi and consequently necroses varies naturally according to the degree of agglutinating activity which they possess. While the most potent sera judging by the reaction in vitro and by the extent and severity of the lesions produced, are those prepared by injecting blood and organs containing a large amount of blood, as the liver and kidney, it is worthy of note that the agglutinative power does not depend entirely on this element, for sera almost as powerful were obtained by injecting bile which contains at best only blood derivatives. On the other hand the various sera prepared by injecting blood free fluids and organs as urine, serum and washed organs, while without power to cause sufficient agglutination in the animal body to bring about the formation of conglutinative thrombi, do cause distinct agglutination *in vitro*. The production of hæmagglutinins therefore would appear to depend on the same principles which govern the production of cytotoxins; that is, upon the similarity in part at least, of the receptor (chemical) composition of the various cells and fluids.[8]

The more powerful sera produce multiple liver lesions almost uniformly when administered in doses of 1:1000 to 1:500;[9] smaller doses (less than 1:1000) may produce necroses, but are usually without effect; large doses (1:500 to 1:300) usually cause death within a few hours. This last result, however, has occurred only with the use of sera produced by injecting blood and unwashed adrenal. In this regard it is of interest that the serum of an animal receiving blood in doses of 0.1 cubic centimeter is as powerful as that of animals receiving doses of five cubic centimeters. The serum of animals receiving washed blood is as potent as that of those receiving defibrinated blood. The power of unwashed adrenal serum to produce liver necroses was but slightly less

[8] For a consideration of this subject and also for a description of the cytolytic action of the various sera here mentioned see Journal of Medical Research 1904, xii, 1. Only the agglutinative action of the sera and the lesions produced in the liver will be considered in this communication.

[9] This method of indicating the dose refers to the relation between the amount of serum injected and the weight of the animal. Thus 1:1000 indicates that an animal weighing 5000 grammes received 5 c. c. of serum or 1 c. c. to 1000 grammes of body weight.

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than that of sera prepared from blood. Unwashed liver and kidney sera and serum prepared by injections of bile caused liver necroses in the same doses as did the above sera, but had no lethal effect. On the other hand, washed liver serum, the only one of this group (sera prepared from washed organs) to cause necroses, did so only when administered in very large doses (1:266), and had no lethal action. Heated sera suffered no loss of agglutinating power.

The necroses produced by these various sera develop in from twenty-four to forty-eight hours. They are usually widespread, closely massed and often confluent. The surface of the liver presents a mottled appearance; small, irregular, yellowish brown or greyish yellow non-elevated areas being sharply outlined by the deeply congested normal substance of the liver. When the congestion is intense the necrotic areas appear depressed owing to the swelling of the congested liver surrounding them, and fine points of hæmorrhage may be seen. On section the brownish yellow areas have a distinct hyaline appearance. The distribution of these lesions is almost always superficial, few necroses being found more than half a centimeter below the surface. When the distribution is not so diffuse, the more prominent lesions are at or near the free edges of the lobes and occasionally limited to the smaller lobes about the gall-bladder. All sera produce uniformly the same type of lesion, though not always the same degree of destruction.

Histology—The necrotic lesion involves the greater portion of a lobule, often the adjoining portions of several lobules. Most frequently the necrosis is in the peripheral portion of the lobule, but occasionally the central zone is involved. The relation to the portal vessels is striking, the altered areas frequently entirely surrounding the portal vessels. The necrosis is hyaline in character, the cells stain poorly with eosin, thus being sharply marked off from adjacent unaltered cells. The nuclei may be fragmented, but more commonly are shrunken and irregular, and often fail entirely to take the stain. Leucocytic infiltration seldom occurs. The capillaries in the midst of these areas are tightly packed with red blood corpuscles. In some capillaries the cells are loosely arranged, but in others

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homogeneous more or less cylindrical cast-like masses of coalesced cells are seen. The endothelium of the capillaries is usually unaltered and accumulations of endothelial cells do not occur. An occasional endothelial cell or polymorphonuclear leucocyte may be found in the midst of these masses, but are never present in considerable numbers. In the smaller portal veins adjacent to the necrotic areas larger ovoid or coalesced masses are seen. These may entirely fill the vessel, though usually a few loose red cells may be found at the periphery. The appearance of these masses is not constant. All contain granular and hyaline areas; in the majority the centre is granular and the periphery hyaline, but frequently this arrangement is reversed. In some, the transition from normal corpuscles to irregular, distorted or varicose corpuscles and finally to hyaline and granular masses may be seen. The hyaline areas upon close examination may be resolved into a tangled mass of irregular varicose threads, representing apparently greatly distorted and elongated corpuscles. Adherent to the walls of the larger vessels distinctly hyaline masses with stalactite-like processes may occasionally be seen. These are apparently of the same origin as the smaller thrombi. Fibrin does not enter into the formation of these thrombi, though the detection of finer threads of fibrin is rendered difficult by the tendency of the altered corpuscles, especially after Zenker hardening, to take the fibrin stain. Fibrin threads may occasionally be found at the periphery of the larger thrombi, but I have never seen them in connection with the smaller plugs.

Taking advantage of the fact that an interlobular vein supplies adjacent portions of several lobules, it has been possible, especially in serial sections, to demonstrate a relation between a thrombus of such a vein and necrosis of the peripheral portions of the lobules in direct relation to it. Also in areas of extensive necrosis involving all but the hepatic vein zone of many lobules, the portal terminals were found uniformly occluded. While it is possible for the capillary thrombi within the lobule to cause necroses the more important plugging occurs, I believe, in the perilobular veins or the branches from which they originate. The anatomical relation of the agglutinated corpuscles to the lesion, in the absence of bacteria,

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phagocytic cell or fibrin thrombi, conclusively indicates that the necroses are due to this obstruction of the smaller veins.

In some animals dying within a few hours after the injection of large amounts of serum (1:400 to 1:500) an extraordinary condition consisting of extreme congestion of the vessels and disorganization of the liver cells was found. Vessels of all sizes were widely dilated and filled with agglutinated corpuscles, while the pressure exerted caused a narrowing of the columns of liver cells with more or less displacement. In one instance the pressure was so great that complete disorganization of the liver substance had occurred. This destruction was so extreme that the histological picture, large sinus-like spaces separated from one another by this compressed and irregularly arranged columns of hepatic cells and filled with closely packed agglutinated and more or less distorted red blood corpuscles, was most suggestive of a cavernous angioma with thin trabeculæ. In this early lesion the liver cells stained poorly, but no distinct necroses were found in animals dying within eighteen hours. The smaller doses, less than 1:1000, on the other hand, never produced changes in the liver other than an occasional slight congestion.

In connection with these lesions the following questions naturally occur. Why do not similar extensive thromboses occur in other organs? Why do necroses occur almost exclusively at the periphery of the liver and why are they limited practically to the portal area? Capillary thrombi do occur in other organs, especially in the glomeruli of the kidney, the periphery of the lung, in the adrenal and in all these locations they may be accompanied by minute hæmorrhages. Their occurrence is, however, infrequent and unaccompanied by necrosis, except possibly in the glomerulus of the kidney. That they do not occur more frequently is probably due to peculiarities in the circulation in the various organs. It is possible that the slow circulation of the portal system allows the formation of larger masses of agglutinated corpuscles than could form in the rapid flow of the other organs; while on the other hand the narrow capillaries of the liver are more readily occluded. The first of these factors would also explain the greater frequency of the lesion in the portal vein area of the lobule. The more frequent involvement of the superficial

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portions of the liver can only be explained by Boxmeyer's assumption that the blood supply of this portion of the liver is less complete, and the collateral circulation less perfect than in the deeper portions of the liver.

Attempts to Demonstrate the Mechanical Nature of the Thrombosis.—As the sera, with one exception, used in these experiments was hæmolytic, and as several possessed other cytotoxic constituents, it became necessary to rule out the direct action of these cytotoxins upon liver cells and also the possibility of an obstruction of the circulation by the remains of hæmolysed red blood corpuscles. Several observations bear on this point and support the theory of mechanical obstruction by agglutinated corpuscles. In order to definitely determine that an agglutination similar to that seen *in vitro*, takes place in the circulating blood of an animal receiving an agglutinative serum, the blood of a dog was examined four minutes after the injection of serum in the dose of 1:350. Blood taken quickly from the heart, the superior vena cava, and the cut surface of the liver, and diluted with salt solution showed abundant coalesced masses of red blood corpuscles. Upon standing, a light jelly-like clot formed with a supernatant fluid containing distinct agglutinated masses not readily disintegrated by agitation. Microscopically these masses, which varied in size, were seen to be composed of from twenty to seventy or more red corpuscles many of which were distorted or elongated and often so fused together as to be indistinguishable one from the other. In another instance twenty-four hours after injection (dose 1:985), masses of the same character were found in blood from the cut surface of the liver. Here the cells were so fused together that the outlines of individual cells could not be recognized.

That agglutinin alone is the important factor in producing these necroses is shown by experiments with serum prepared by injecting bile. This serum, while powerfully agglutinative, unlike the other sera used, has no hæmolytic power. It causes, however, in doses of 1:700 widespread lesions of the liver similar to those described above. Attempts to render other sera hæmolytically inactive by heating have been unsuccessful. Animals receiving such sera develop hæmoglobinuria and the

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renal changes which usually follow the administration of a hæmolytic serum, as well as typical liver lesions, the result of the action of the agglutinin.

As a somewhat imperfect test[10] of the mechanical nature of the thrombosis, attempts were made to produce necroses by injecting agglutinated masses of red corpuscles freed of the excess of immune serum by repeated washing. These masses were prepared by agglutinating dog's blood *in vitro*, and washing hastily in several changes of salt solution. Agglutinated masses, thus prepared, injected into the mesenteric vein in doses of five to ten cubic centimeters seldom produce necroses and those which do occur are not of the same type or so numerous as those produced by the injection of agglutinative serum. They represent the type of granular necrosis with nuclear fragmentation rather than the hyaline type and are very few in number. Associated hyaline thrombi were found only occasionally. In all these experiments the spleen contained a very large amount of altered blood pigment, indicative of the fate of the injected cells. I consider the results of these experiments to be of little significance one way or the other, for the injection of five or ten cubic centimeters of agglutinated corpuscles, an amount readily destroyed in the animal, is in no way comparable to the extensive agglutination resulting from the cumulative action of ten to twenty cubic centimeters of agglutinative serum.

Various controls as the injection of defibrinated normal dogs blood, washed hæmolyzed dogs corpuscles, the blood and the clear serum of dogs in which the liver lesions had been produced, and normal rabbits serum have been uniformly negative.

Effect of Repeated Injections.—The severity and extent of the lesions produced by the injection of agglutinative serum suggested the possibility of producing, by repeated injections, conditions analagous to acute yellow atrophy or the more acute forms of cirrhosis. With this object several animals have received serum intravenously at intervals of one to three weeks. Thus far no permanent lesions have been found in animals which have been killed at the end of seven weeks after

[10] This condition of this test is not perfect, for the haemolytic amboceptors of the serum are of course fixed by the red corpuscles.

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receiving three injections. Indeed, from a study of the liver necroses in a small number of animals which have been allowed to live more than a few days, there is very distinct evidence that these lesions are completely repaired. The observations upon this phase of the subject are, however, too few to warrant a definite statement at this time.

May Agglutinins be a Factor in the Production of Liver Necroses in Man?—In considering this question it is not necessary to go into the general literature bearing upon the etiology of liver necroses. That these lesions may be produced by the direct action of bacteria (B. tuberculosis, B. pestis, and the pyogenic cocci) is well known. Mallory[11] has shown very conclusively that they may be due also, especially in typhoid fever, to occlusion of the capillaries by clumps of phagocytic endothelial cells with or without associated fibrin coagula. That a strong toxin in the circulating blood may produce the so-called central necroses is also indicated by his investigations. There remain, however, many focal necroses which cannot be satisfactorily explained. Associated with such are frequently found capillary thrombi described as hyaline or fibrinous. It seems probable that these, in view of the facts set forth in this communication, may be agglutinative red blood corpuscle thrombi and the essential element in causing the necroses with which they are associated. Flexner and Boxmeyer working independently came to the conclusion that the so-called hyaline thrombi were composed of fused red blood corpuscles. Flexner found such thrombi in the intestine of typhoid, the stomach of carbolic acid poisoning and in broncho-pneumonia; and in the rabbit produced them experimentally by the injection of agglutinating substances as ricin, ether and dog's serum; Boxmeyer found them in the liver necroses of experimental hog cholera. It is significant that the latter could readily distinguish necroses due to such thrombi from those due to phagocytic cell thrombi. Many of those who have studied hyaline thrombi, state that they are composed of fused and altered red blood corpuscles, but do not explain the mechanism of the fusion. Ziegler's[12] opinion that they are formed largely from the colorless

[11] Mallory. *Journal of Exper. Medicine*, 1898, iii, 611; *Journal of Medical Research*, 1901, vi, 264.

[12] Ziegler. *General Pathology*, Eng. Ed., 1899, p. 122.

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elements of the red blood cells, is of interest in view of our newly acquired knowledge of agglutination and hæmolysis.

In attempting to bring agglutinative thrombi into relation with liver necroses in man it is necessary to explain the origin of the agglutinin. The possibility of its development as a bacterial product in the course of infectious diseases, naturally suggests itself. It is well known that a considerable number of bacteria produce hæmolysins, and it has been demonstrated that a few produce also hæmagglutinins. This agglutinating power is possessed also by several poisons not of bacterial origin. In this connection it is significant that most of the conditions in which hyaline thrombi have been described are of bacterial etiology as hog cholera, typhoid fever, bronchopneumonia, diphtheria and infections with the pyogenic cocci; or intoxications as poisoning by ergotin, corrosive sublimate, carbolic acid, ricin and abrin. Of considerable interest in this connection is Flexner's reference to the occurrence of agglutinative thrombi in the liver lesions of eclampsia. The occurrence of hyaline thrombi in the vessels of the rabbit's ear, after freezing, points also to an injury of red cells leading to agglutination.

It seems probable that the application of experimental methods may demonstrate that agglutinins may be formed in various infectious and toxic conditions in sufficient quantity to cause agglutinative (hyaline?) thrombi with the development of liver necroses and possibly other lesions. Experiments, now in progress, with the products of antolyzed bacteria indicate the presence of such a body in sufficient amount to produce agglutinative thrombi.

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Reprinted from ALBANY MEDICAL ANNALS, November, 1904

CONCERNING HEMAGGLUTININS OF BACTERIAL ORIGIN AND THEIR RELATION TO HYALINE THROMBI AND LIVER NECROSES.*

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AND

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Elsewhere, one of us[1] has described the hemagglutinative power of various cytolytic immune sera and the relation of the red blood corpuscle thrombi (hyaline thrombi) resulting from the injection of such sera to focal hyaline necroses of the liver. The distinct character of the liver lesions thus produced, and the fact that they could be explained only by the presence of agglutinated red blood corpuscle thrombi, suggested the possibility that similar lesions occurring in various infectious diseases might be due to the development of hemagglutinins of bacterial origin. In order to test this supposition we have attempted to demonstrate the presence of hemagglutinins in filtrates of bacteria treated in various ways, and, by the injection of the same into animals, to produce agglutinated red blood corpuscle thrombi and associated liver necroses.

It is not our intention to go into the general literature of these subjects, but merely to touch upon those points which relate to infectious conditions. The more important views concerning liver

*This study has been conducted under a grant from the Rockefeller Institute for Medical Research. Published also in the *American Journal of the Medical Sciences*, October, 1904

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necroses may be found in the papers of Flexner,[3] Mallory,[3] Boxmeyer[4] and Opie.[5] That the so-called hyaline thrombi may be composed of altered and fused red blood corpuscles we consider to be definitely established. The recent studies of Flexner,[6] Boxmeyer, and Pearce offer conclusive evidence of such origin and support the earlier observations of Klebs[7] and Ziegler.[8] The occurrence of hyaline thrombi in connection with various infectious and toxic conditions has been emphasized by Welch,[9] who, in his summary of the literature, mentions particularly infections with S. pyogenes aureus and B. cholerae suis, and offers a suggestion concerning their origin from red blood corpuscles. In a later discussion[10] of the subject he brings forth the hitherto unpublished observations of Fisher concerning the plugging of small vessels by agglutinated red cells as the result of injecting typhoid bacilli, and calls attention to the evidence in favor of the interpretation of many of the hyaline thrombi as derived from fused red blood corpuscles. Other important observations are those of Flexner, who found similar thrombi in the intestine of typhoid fever, in bronchopneumonia and in experimental diphtheria; and also of Boxmeyer, who could distinguish, in the livers of rabbits dying of experimental hog cholera, between necroses due to endothelial cell thrombi and those due to agglutinated red blood corpuscle thrombi. The hyaline thrombi occurring in various intoxications, due to either organic or inorganic poisons, and in toxic conditions of doubtful origin, as eclampsia, are undoubtedly of similar nature; but as they do not come within the scope of this study, will not be further considered.

Of considerable historical interest in connection with this question of the occurrence of red blood corpuscle thrombi in the course of infectious diseases are the observations of Hueter,[11] made in 1873. As the result of his studies, to which attention has recently been called by Welch,[10] Hueter came to the conclusion that clumping of red blood corpuscles, causing permanent or transient occlusion of capillaries and small vessels ("glöbulose Stase und Embolie") occurred not uncommonly in septic and other fevers. His theory that this phenomenon constituted the underlying basis of fever has never gained acceptance, but the observations are of interest in connection with our recently acquired knowledge of bacterial hemagglutinins. v. Recklinghausen[12] considers this globular stasis of Hueter to be analogous to a condition found in

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the capillaries after transfusion of alien blood, and which he describes as an "agglutination" of red blood cells.

In planning this investigation it was evident that as necroses of the liver are most frequently associated with infections by the bacillus of typhoid fever and the bacillus of hog cholera, the bulk of the work should be done with these organisms. In order, however, that no opportunity might be lost, the literature dealing with bacterial hemolysins was examined in the hope of finding reference to organisms which produced also hemagglutinins; of twenty-nine such investigations[13] but six[14] refer to the production of hemagglutinins by bacteria. Kraus and Ludwig found that bouillon cultures of S. pyogenes aureus and Vibrio Paris had the power of agglutinating red blood corpuscles *in vitro* in from ten to twenty-four hours at room temperature. The mass which settled at the bottom of the tube was seen upon agitation to be composed of small clumps of red blood corpuscles which could not easily be disintegrated. The agglutinin they considered to be independent of the hemolysin; but, on the other hand, they state that organisms which do not hemolyse also do not agglutinate. Small amounts of the cultures caused agglutination without hemolysis. Volk and Lipschütz, working with staphylolysin and vibriolysin, describe agglutination in connection with incomplete hemolysis of rabbits' blood, but did not observe it with other bloods. Volk, as a result of his observations, comes to the conclusion that agglutination is due not to a specific body, but to non-isotonicity of the fluid. Calamida states that no agglutination precedes the hemolysis caused by bouillon cultures of the chicken-cholera bacillus. Flexner mentions agglutinins of low activity in filtrates of B. pyocyaneus, B. typhosus, and S. pyogenes aureus. Kayser, in his study of colilysin, observed a clumping of red cells in connection with incomplete hemolysis, but not when complete solution occurred. Of greatest interest, however, and very suggestive, is the observation of Eisenberg,[15] who found the blood of an individual with a generalized pyocyaneus infection to be both auto-agglutinative and iso-agglutinative.

As the result of this survey, it seemed advisable to utilize B. pyocyaneus and S. pyogenes aureus in addition to B. typhosus and B. cholerae suis; and these, with B. dysenteriæ and S. pyogenes, constituted the group of organisms finally selected for study.

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METHODS. In previous attempts (Reed,[16] Flexner, Mallory, and Boxmeyer) to produce liver necroses by the injection of microorganisms, either the living culture, grown in the ordinary way, or its filtrate has been used. With the use of the former it has been difficult to distinguish between the direct action of the organism and the effect produced by its toxin; with the latter the action of intracellular toxins has been excluded. In our experiments the direct action of the microorganisms has been eliminated by the use of filtered fluids, and an attempt has been made to obtain the intracellular constituents of the bacterial cells by the utilization of methods destined to cause its disintegration. Various writers have described methods by which the bacterial cell is destroyed and its receptors liberated. Of these methods we have tried, with certain modifications, the processes of autolysis described by Conradi,[17] Neisser[18] and Shiga, and Brieger and Mayer.[19] The various organisms have been grown for twenty-four to seventy-two hours on agar in large flat flasks having a surface of twenty by eight centimetres. The growth on several flasks, usually three or four, has then been scraped off, subjected to 55° C. for forty-five minutes, and placed in tubes containing 0.85 per cent. salt solution at a temperature of 37.5° C. for two to three days. In some instances the fluid has stood for longer periods, varying from one to seven weeks. The fluid has then been filtered (Chamberland B. and F.) and injected intravenously into animals after testing its agglutinative power *in vitro*. At various stages of the process suitable controls were made to demonstrate absence of contamination and the efficiency of the filters.

In addition to this method of growing the organism, an attempt was also made to stimulate the production of hemagglutinin by previously growing the organisms in media containing red blood cells. This method was suggested by the theory of "bacteriogenic cytotoxins," advanced by Welch in his Huxley Lecture: "Certain substances of the host of cellular origin, assimilated by the parasites through the possession of haptophore groups with the proper affinities, become anchored to receptors of the parasitic cell, which, if not too much damaged, is thereby simulated to the overproduction of like receptors; these excessive receptors of the parasite, if cast off into the fluids or the cells of the host, then constitute intermediary bodies, etc." The writer further states: "by a similar mechanism it is possible that parasites may be stimulated to the

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production also of antibodies other than cytotoxins, such as various agglutinins, precipitins, antienzymes—all adjusted against the host."

Assuming that if this hypothesis might apply to organisms growing in living cells or fluids, it might hold also for those grown on cells outside the body, typhoid and hog cholera bacilli have been grown in various blood preparations. These include both defibrinated and washed blood added in various proportions to salt solution, and fresh sterile rabbits' organs. The period of growth in the various blood mixtures varied from twenty-four to seventy-two hours; in some instances inoculations into fresh blood solutions or upon fresh organs being made on each of three successive days. The sterile organs were prepared according to the technique described by Flexner.[20] By these various methods it was hoped that the organism would be stimulated to produce agglutinins and that this power would be retained during the subsequent growth on agar, giving in the finished autolyzed product, a fluid of appreciably augmented agglutinating power. Observations supporting this theory have been made by Marmorek and by Simon, who found that streptococci grown in media composed of leukocytes alone, or with bouillon added, secrete a toxin of considerable power. Simon[21] believes that the streptococcus in order to secrete toxin must meet a certain resistance to its development, and that this resistance is furnished by something in the leukocytes. This explanation, put in the terms of Ehrlich, corresponds to Welch's hypothesis. Our attempts to produce free agglutinin receptors by growing the organisms in blood we consider analogous to Simon's method of producing toxin by growth in leukocytes.*

Another method employed was the growth of an organism in heated rabbit serum. This was suggested by the observation of Besredka,[22] that the streptococcus produces an hemolysin when thus grown.

RESULTS. The tests for agglutination were made by adding nine parts of the various filtrates to one part of blood. Observations were made at room temperature and at 37.5° C. at varying

*Another point in favor of this theory of bacteriogenic antibodies is the observation of Theobald Smith (verbal communication) that recently isolated cultures of the hog-cholera bacillus have a greater power to produce liver necroses than have old cultures. Accepting Boxmeyer's work on the relation of agglutinative red blood corpuscle thrombi to such lesions, the explanation naturally suggested is, that residence in the animal has stimulated the power of the bacillus to produce agglutinin.

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periods up to twenty-four hours. The clumping of red blood corpuscles by bacterial hemagglutinins is of slight degree as compared with that produced by various cytolytic immune sera. The powerful agglutination of the latter is never seen, and for this reason more careful comparison with controls is necessary in order to detect slight differences in reaction. This feeble activity renders it difficult to make definite statements concerning some of the organisms studied. While all (B. typhosus, B. cholerae suis, B. pyocyaneus, B. dysenteriæ, S. pyogenes aureus and S. pyogenes) in the majority of tests, *in vitro,* showed a slight agglutination as compared with controls the effect of filtrates of B. dysenteriæ, B. cholerae suis and B. pyocyaneus was so slight as to be considered doubtful. With other organisms the agglutination was more evident, being most distinct with filtrates of S. pyogenes. Upon microscopic examination (hanging drop) the clumping caused by the streptococcus was always in the form of massive, more or less branching, rouleaux; while with all other cultures an irregular agglutination of a small number of corpuscles was seen. The agglutination due to the streptococcus could be seen after fifteen to twenty minutes, as the corpuscles settled, while with the other organisms it could be seen only upon agitation after a considerable period of time. More definite results were obtained with rabbits' blood than with dogs' blood.

Of unusual interest and very suggestive are the agglutination tests with filtrates of typhoid bacilli previously grown in blood suspensions and on fresh sterile organs; though carried out in but a small number of tests, they appear to be confirmatory of Welch's hypothesis mentioned above. These filtrates, especially those of bacilli grown on sterile organs, exhibit an appreciably greater power of agglutination than the filtrates of organisms grown on agar only.

While no effort was made to study especially bacterial hemolysins, it is of interest that the autolytic products of bacteria as here prepared have never caused hemolysis. This result is in harmony with the observations of Jordan,[23] Williamson[24] and others who hold that the hemolysis produced by many bacterial filtrates (B. typhosus, B. pyocyaneus) is to be explained by the presence of an alkali elaborated in the growth of the organism. The filtrates used in our tests have all been faintly acid to phenolphthalein.

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The animals selected for the injection experiments were dogs and rabbits; the former receiving five to twenty cubic centimetres (dose 1 :1514 to 1 :235) of the filtrates in either the saphenous or mesenteric vein; the latter one to twenty cubic centimetres (dose 1 :1790 to 1 :64) in either the mesenteric or marginal ear vein. In all, twenty-nine injections have been made; in no instance did death occur as the immediate result of the injection. Necroses of the liver occurred in ten of the animals. Two of these we have thought best to exclude because of associated coccidiosis, although the necroses appeared to be entirely independent of the parasitic invasion; another has been excluded also because of the chronic character of the lesion. The remaining seven cases exhibited typical necroses; two occurring in dogs and five in rabbits. These lesions followed the injection of filtrates of the typhoid bacillus in three cases, of the hog-cholera bacillus in three cases, and of the dysentery bacillus in one case. Filtrates of the B. pyocyaneus, S. pyogenes aureus, and S. pyogenes did not cause necroses. These necroses are not always visible to the naked eye, but when seen macroscopically they appear as miliary points, or occasionally as round or oval areas or linear streaks of grayish color, and distinctly separated from the normal liver tissue. They are very few in number compared to those produced by the agglutinins of cytolytic immune sera, and are usually limited to the superficial portions of the liver. Portions of the liver in contact with other lobes or adjacent organs are more frequently involved than the free surfaces. Histologically, the liver cells exhibit a hyalin necrosis, the nuclei being entirely destroyed, or evident merely as faint rings; fragmented or pyknotic nuclei were seldom seen. In many of these areas the vessels are filled with red blood corpuscles more or less altered and fused, and suggestive of hyaline thrombi. This condition, however, is not constant, and is not so evident as in the necrotic lesions produced by cytolytic immune sera. On the other hand, larger vessels, especially the smaller branches of the portal vein, contain typical agglutinative red corpuscle thrombi more or less completely occluding the vessel. Similar thrombi of small vessels have been seen in other organs, as the kidney, spleen, and lymph nodes, but without definitely associated lesions. Other thrombi, as those composed of endothelial cells, fibrin, etc., have not been seen in the liver.

Fatty changes in the liver and kidney, intense congestion of

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the spleen and lymph nodes, and a proliferation of the endothelial cells of the lymph sinuses have been found not infrequently after the injection of typhoid and hog cholera filtrates. A relation between these lesions and the injected fluids cannot, however, be readily demonstrated; the proliferation of endothelial cells, especially, is not infrequent in apparently normal animals. That some serious injury to the kidney is brought about is indicated by the appearance of albumen in the urine after the injection of filtrates of B. typhosus and B. dysentriæ.

The results of the injection of filtrates of typhoid and hog cholera bacilli grown upon blood media, while very suggestive, are not conclusive, owing to the small number of observations. But six filtrates so grown were injected. Filtrates of the typhoid bacillus grown in blood suspensions, while possessing an increased agglutinating power *in vitro,* did not cause necroses upon injection; on the other hand, two different filtrates of the same culture grown for several days on sterile rabbits' organs caused the most extensive lesions observed in the course of this investigation. The bacillus of hog cholera grown in blood suspensions caused, in one instance, lesions in the liver. The attempt to produce necroses with such filtrates has therefore been successful in three of six experiments; while with filtrates of the same organism grown on plain agar necroses resulted in three of twelve attempts. These results are suggestive in connection with the increased agglutinating power observed *in vitro,* but the small number of experiments does not warrant definite conclusions.

Filtrates of B. typhosus grown in heated rabbit serum produced no lesions upon injection into rabbits.

Conclusions. The filtered autolyzed products of a number of bacteria possess hemagglutinins of low activity; the formation of these may be stimulated by previously growing the microorganisms on media containing fresh red blood cells. The injection of these filtrates into dogs and rabbits is followed in some instances by the occurrence of liver necroses with associated fused red blood corpuscle thrombi; like thrombi may occur in other organs. These thrombi are similar in structure to those generally described as hyaline thrombi. The demonstration of agglutination *in vitro* and the association of the fused red cells with the liver lesions suggest a relation of the agglutinin to the lesions. This relation, however, cannot be considered as proven, for it is impossible to exclude the

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effect of toxins acting directly upon the liver cells; on the other hand, the similarity of the lesion to the very definite necroses caused by he powerful agglutinins of cytolytic immune sera strongly supports the possibility of such a relation.

The results observed by us are in accord with the slight potency of the agglutinin obtained. It is probable that methods which cause a more complete disintegration of the bacterial cells, as those employed by Vaughan[25] and by MacFadyan and Rowland,[26] would yield an agglutinin as powerful, comparatively, as the toxins so derived, and capable of producing lesions more analogous to those caused by the agglutinins of cytolytic immune sera.

We present this communication, therefore, not as an attempt to prove that all hyaline thrombi are composed of fused red blood corpuscles, or that all liver necroses are caused by such thrombi, but rather to indicate the evidence in favor of the view that these lesions, in some instances, may be due to bacterial hemagglutinins.

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Reprinted from the ALBANY MEDICAL ANNALS, July 1904

COMPLICATIONS AND DEGENERATIONS OF UTERINE FIBROMYOMATA.

A PATHOLOGICAL AND STATISTICAL STUDY OF TWO HUNDRED AND EIGHTY CASES.

Read before the Philadelphia Obstetrical Society. Published in the Journal of the American Medical Association, 1904, XLII, 1344, (May 21).

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INTRODUCTION

Recent discussions in the surgical and gynecologic branches of the American, British and French medical organizations, indicate a renewed interest in the question of treatment of uterine fibromyomata. This is due largely to facts brought forth as the result of the systematic routine pathologic examination of all "fibroid" tumors. The frequency with which fibroid tumors present degenerations and are accompanied by complications has upset the classical teaching in regard to prognosis and treatment of these growths. More particularly has interest been stimulated in regard to the so-called "malignant degenerations," as is evidenced by the prominent place which carcinoma and sarcoma occupy in recent publications on myoma. At present, however, the results of pathologic studies are not definitely collected, and there is a lack of statistical comparison. The importance of bringing together such results is evident, for the question of operative interference and extent of operation must depend

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on information derived from combined clinical and pathologic reports. In regard especially to the extent of operation are the results of pathologic investigation of value. While in the removal of a benign tumor it is without doubt ideal that the patient should suffer as little mutilation as possible, still that operation must be done which offers the least danger, and at the same time takes into consideration the various attendant complications. On this point recent investigations indicate that the complications of myomata are by no means to be lightly considered.

Aside from the tumor itself, the adjacent organs must be taken into account. The question of the condition of the ovaries is important from the fact that in supravaginal hysteromyomectomy the trend of opinion among gynecologists is that an ovary should be left in order to ameliorate the severe menopausal symptoms sometimes produced by complete ablations. For this reason the microscopic study of these organs is important in order to determine the frequency of disease of the ovary in connection with myoma.

Also, after hysteromyomectomies and myomectomies, the possibility of infection from a diseased tube is of importance, not only as concerns the union of the wound, but also as regards the mortality of these operations. Hence the examination of the tubes for salpingitis, pyosalpinx, etc., is of no slight value.

In the study which is here presented, an attempt has been made to determine the frequency of the various degenerations and complications and to base thereon certain general conclusions concerning treatment.

GENERAL LITERATURE

Since Martin[1] in 1888 made his study of degenerations in 205 cases of fibromyomata, others have reported similar series, notably Noble,[2] 258 cases; Cullingworth,[3] 100 cases; Mary Scharlieb,[4] 100 cases, and Frederick,[5] 125 cases. Combined, these make 788 cases available for the classifica-

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tion as to degenerations. There is some slight difference in the classifications of the five writers, but by taking certain liberties with their tables,* the degeneration may be summarized as follows:

Fatty degenerations	7
Calcareous infiltration	11
Necrosis	55
Cystic degeneration	34
Telangiectasis	46
Sarcoma	17
Associated carcinoma cervicis	15
Associated carcinoma corporis	17
Myxomatous (edematous)	8
Associated syncytioma [6]	1

(Total number of cases, 788.)

Martin has not estimated his complications; so for the purpose of that classification only the series of Noble, Cullingworth, Mary Scharlieb and Frederick are available They are as follows:

Appendicitis	13
Hydrosalpinx	41
Hematosalpinx	2
Ovarian cyst	32
Dermoid cyst	5
Ectopic pregnancy	4
Papillary carcinoma of ovary	2
Pyosalpinx	18
Salpingitis	10
Abscess of ovary	7
Tubo-ovarian abscess	1
Dilated ureters and hydronephrosis	1
Dilated ureter, hydronephrosis and pyelitis	1
Parovarian cyst	3
Cystic ovaries	18
Hematoma of ovary	1

*In this table associated tumors are arbitrarily included. Martin's ten cases of suppuration are placed under necrosis. Noble's case of syncytioma is retained, although there is some doubt from the pathologic report as to whether there was a fibroid associated with the new growth. This tumor was twice reported. The following extract is from the second publication, pathologic report by Dr. Babcock: "In the early description of the growth it was described as a sarcomatous or endotheliomatous degeneration of a fibroid tumor; but restudy gives no evidence that fibromuscular tissue is present more than would accompany the growth of the syncytial tumor. It is believed that this is a primary syncytioma malignum in a uterus not the seat of any other tumor."

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Tubercular peritonitis	1
Universal adhesions	22

(Total number of cases, 583.)

In making this compilation a great difference in classification was apparent. Frederick and Mary Scharlieb alone mention cystic ovaries. Cullingworth in his 100 cases does not mention salpingitis. Many complications of a purely clinical nature, as retroversions of the uterus, etc., have been eliminated in order to bring the classification in accord with that of this paper.

In a more recent publication, Daniels[7] in 124 cases found pathologic lesions in the appendages or their immediate neighborhood in seventy-two; in seventy cases of complicated fibromyomata, lesions were confined to the ovary in twenty-eight, to the tubes in twelve, and involving both in thirty.

Marscher[8] in twenty-two cases of myomata found ectopic pregnancy in one and suppurative diseases of the appendages in four.

Bond[9] reports fifty cases, in which eight had tubal disease, which he claims was due mainly to infection from miscarriage.

Hunner[10] in a series of 100 consecutive cases occurring in Kelly's service found pyosalpinx or tubo-ovarian abscess in six cases, hydrosalpinx or perisalpingitis in fifteen cases and ovarian cysts in nine cases. There was found in association malignant disease in seven cases; sarcoma in two, adenocarcinoma of the fundus in three, and squamous carcinoma of cervix in two.

Other writers have reported smaller series of cases or series devoted to one complication as appendicitis[11] or salpingitis[12]. As these reports do not include all complications they have not been quoted.

From this summary it will be seen that the complications of fibromyomata are many and varied. It will be noted that tubal complications form a very large percentage in Daniel's series, while in the combined series they are not prominent; also in the latter series pyosalpinx is numerically greater than salpingitis. This may, I think, be explained by the fact that

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the earlier writers did not have a complete microscopic examination of the condition of the tubes. Frederick mentions cystic ovaries which occurred in about fourteen per cent. of his cases. Mary Scharlieb estimates ovarian cysts and cystic ovaries together as twenty-three per cent.

In regard to associated malignant tumors in the combined series, carcinoma occupies a relatively high place. No distinction is made between "sarcomatous degeneration" of a myoma and of sarcoma associated with myoma except in Martin's paper. Of the more recent publications on sarcomatous degeneration of fibroids, Baker and Graves[13] publish thirty-three cases of fibroid tumors, in which three were sarcomatous. The percentage is truly large; but this is similar to the findings of Ulesko-Stroganowa,[14] who reported before the Russian Society for Obstetrics and Gynecology, March 22, 1902, 100 cases of fibromata with ten cases of malignant degeneration. From the description these are evidently divided into two groups, leiomyoma malignum and true sarcoma. It is not quite clear what is meant by the former. In the discussion which followed, her views were generally opposed. From the abstract of her paper it is impossible to say how many of these were really sarcomatous.

Tate[15] and Bertha Van Hoosen[16] each report a case of sarcomatous degeneration of fibromyoma, which will be referred to later under the special heading.

From these papers it will be seen that "sarcomatous degeneration," while not common, is sufficiently so to merit further study; first, in regard to its frequency, and second, as to whether it is a true transformation of a myoma or merely an associated but independent growth.

MATERIAL

The material on which this study is based* represents seven years' service of a general hospital (Albany Hospital),

*I wish to express my thanks to the operators from whom these cases came, more particularly to the surgeons of the Albany Hospital. I also wish to express my gratitude to Dr. Blumer, late director of the Bender Laboratory, and to his assistants, whose conscientious routine examinations and exhaustive records have made this report possible. I also wish to express my sincere thanks to Dr. R. M. Pearce, present director of the laboratory, for constant assistance and encouragement.

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and includes all myomata removed during that time. Complete gross and microscopic examinations have been made in all cases. The series also includes 26 cases in which myomata were found at autopsy.

SUMMARY OF 280 CASES OF FIBROMYOMATA.

Character:—	
Single	110
Multiple	170
Small	79
Medium	59
Large	99
Very large	43
Subserous	67
Interstitial	85
Submucous	23
Combined	105
Degenerations—	
Slight hyaline	18
Moderate hyaline	32
Marked hyaline	19
Hyaline and calcareous	8
Calcareous	14
Calcareous, necrotic, hemorrhagic	2
Cystic	8
Myxomatous	4
Hemorrhagic	6
Necrotic	4
Necrotic and hyaline	3
Necrotic, cystic, infected	1
Adenomyoma	6
Associated with adenocarcinoma	6
Associated with squamous cell carcinoma of cervix	2
Sarcoma	3
Deciduoma malignum	1
Complications—	
Ovarian cysts	15
Parovarian cysts	2
Cystic degeneration of ovaries	55
Tubo-ovarian cyst	1
Calcification of ovary	1
Ovarian fibroma	2

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Ovarian carcinoma	2
Salpingitis	38
Salpingitis and hydrosalpinx	3
Salpingitis and tubo-ovarian abscesses	3
Pyosalpinx	5
Pyosalpinx and tubo-ovarian abscesses	2
Extra uterine pregnancy, salpingitis and hydrosalpinx	1
Hydrosalpinx	6
Hydrosalpinx and tubo-ovarian abscess	1
Autopsies—	
Total number	26
Deaths due to tumor	2

PATHOLOGY

Character.—All these variations in fibroid tumors are familiar to operators and pathologists. "Multiple" in this series is taken to mean more than one tumor. The division as to size has been based on the following scale: Small, up to four centimetres; medium, four to eight centimetres; large, eight to sixteen centimetres; very large, above sixteen centimetres in diameter. In multiple tumors the diameter of the largest tumor was taken as the determining factor. The largest tumor noted weighed ninety pounds, and measured roughly 50x40x20 centimetres. The tumor was single, showed considerable necrosis and calcareous degeneration, and caused pressure symptoms which brought on the death of the patient. It was removed postmortem. Several other tumors were noted between forty and fifty pounds. It will be noted that 142 tumors measured more than eight centimetres in diameter.

The analysis as regards position was not easy, as it is not always plain into which of the classes a tumor should go. I regret that there is excluded a most important class of broad ligament fibromyomata, of which the data at hand would not allow a proper estimation.

By "combined" is meant multiple tumors, one each of which may be classed in one of the divisions. Thus it is

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seen that there are sixty-five multiple tumors which fall into one class (always interstitial or subserous), and 105 multiple which fall into at least two classes.

In one case of multiple fibromyomata a medium-sized fibroid had become detached from its pedicle and lay retroperitoneally, being nourished by the mesenteric vessels. Similar cases have been reported by Alban Doran[17] and others.[18]

The comparative infrequency of submucous myomata is noticeable.

Simple Degenerations.—In tumors of such size (142 above 8 centimetres diameter) it is remarkable that a large number with degeneration, particularly with hyaline degeneration, was not met with. The combination of hyaline and calcareous degeneration in eight cases is of interest. It would seem that the tendency of these tumors is to undergo progressive hyaline change going on to calcareous degeneration.

The twenty-three examples of calcareous degeneration existed in old women, but one being below fifty. These varied in consistence from those of the "Wombstone" type, ten centimetres across, to those with discrete, moderate calcareous deposits.

In the consideration of cystic degeneration, as Alban Doran[19] shows, a distinction should be made between true cystic degeneration and necrosis going on to cavity formation. In this series, however, his standard of judgment that a "fibroid is not truly cystic unless it includes a cavity containing half a pint of fluid," has not been adhered to, but tumors with smaller cavities have been judged as truly cystic. There were no cysts of large size found, the largest containing approximately 1,000 cubic centimetres of fluid. Cystic degeneration is more especially interesting from the fact that of Graves' four cases of cystic degeneration three were sarcomatous, evidently a necrosis going on to cyst formation. Mary Scharlieb's series shows six cases of sarcomatous degeneration, and of these three were cystic.

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Necrosis and Inflammation.—All stages of inflammation and necrosis were noted. Necrosis occurred mainly in large subserous tumors, and was evidenced, on section, by brownish-yellow areas. There was usually considerable associated odema. In four cases this went on to liquefaction of the central area. It is interesting to note in regard to the possibility of infection that two cases were associated with salpingitis and two with hydrosalpinx. One large submucous tumor with multiple interstitial nodules was necrotic and sloughing. In all cases of sarcomatous degeneration, hemorrhage and necrosis were noted.

Adenomyoma.—The percentage of these tumors is about that usually found. They offered in this series nothing of special remark in the gross appearance. One showed marked hyaline change and one calcareous degeneration.

Malignant Changes.—Sarcomatous degeneration was found in three cases. There was no definite appearance by which these sarcomatous changes could be recognized. The main characteristics were necrosis, with broken-down areas and discolored spots from recent and old hemorrhages. A yellowish-white glistening growth could be distinguished in one case infiltrating the muscle and surrounding the necrotic areas. During the period from which these reports were taken six cases of sarcoma of the uterus occurred, in addition to these three cases of sarcomatous degeneration of uterine fibroids.

In case one it was possible to make a diagnosis in the gross specimen, as the disease had infiltrated the uterine tissue and gave a semi-necrotic appearance with irregular, hemorrhagic, pinkish areas devoid of fibrous arrangement, and a shell of malignant tissue infiltrating the tumor.

Cases two and three were also necrotic, soft and friable, and in the macroscopic examination were taken for necrotic fibroids.

Chorio-epithelioma infiltrated one case of fibroid tumor.

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This is, so far as is known, the first authentic instance of such invasion reported. Complete reports of these four specimens from the records of the Bender Laboratory follow:

CASE I.—Mrs. M. N. Specimen consists of uterus with tubes and ovaries. One tube and ovary are separate from the rest of the specimen, the tube having been amputated at the junction with the uterus.

Uterus.—The uterus is greatly enlarged and measures 19 cm. long and about 14 cm. in diameter. Except for an irregular area about 7 cm. in diameter corresponding to the fundus, the peritoneal surface is everywhere covered with firm adhesions. Near the superior surface of the fundus are two globular tumor masses the size of a cherry, which are attached to the body of the uterus by a slender pedicle of peritoneum and fibrous connective tissue. Near the above tumor can be seen a pea-sized submucous tumor similar to the above. On section these tumors are pearly white with fine whorls of connective tissue. Adjacent to the origin of the attached tube projects a tumor mass about 3½ cm. in diameter which is soft and on section shows a thin capsule with central contents similar to that of the cavity of the uterus. On section the cavity of the uterus is found to be filled with a necrotic mass, the core of which is the size of an orange, and of a pinkish, yellow color with the consistency of liver tissue. This central mass shows whorl-like markings suggesting the cross-section of a large fibromyoma. Extending from the central core and infiltrating into the muscular coat is a stratum of extremely friable tissue from 2 to 4 cm. in thickness. This stratum is throughout semi-necrotic and shows irregular hemorrhagic areas, while at the outer border is an irregular zone which on section presents a jelly-like whitish glistening surface. The muscular coat of the uterus is under considerable tension, retracting rapidly when cut. This muscular coat has an average thickness of about 5 mm., but in many places is not over 2 mm. in thickness. The boundary between the muscular and semi-necrotic mass is nowhere sharply drawn, so that the muscular coat appears to be infiltrated by the mass lying beneath it. Near the fundus of the uterus, the muscular wall is much thicker than elsewhere. On section there is disclosed a definitely encapsulated tumor mass the size of a hen's egg which readily separates from the capsule and presents on section a soft, dark red, irregularly mottled surface. It is connected by a broad isthmus to the mass occupying the cavity of the uterus.

Tubes.—The attached tube is markedly congested, but otherwise apparently normal. Opposite tube is the same.

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Ovaries.—The attached ovary is cystic throughout, having numerous cysts ranging from the size of a pigeon's egg to that of a pea, the substance of the ovary being crowded to one side. Opposite ovary shows very many cysts ranging from 2 to 10 cm. in diameter. These cysts contain clear straw-colored fluid.

Anatomic Diagnosis.—Sarcoma of uterus with necrosis and hemorrhage.

Microscopic Description.—Tissues, uterine wall, ovary, polypoid tumor described in gross description. Uterine wall: Sections taken through portion described as capsule in gross description show smooth muscle infiltrated with masses of spindle-shaped cells having large clear staining vesicular nuclei and little protoplasm. Among these cells are seen large irregular cells, the nuclei of which have a lobulated outline. Indistinct mitotic figures are seen in some of the cells. These cells have an utterly lawless arrangement, and deeper in the sections they form a continuous mass containing numerous thin walled blood vessels. Many of the sections show hemorrhagic areas with red blood corpuscles in various stages of degeneration. Some sections show simply masses of necrotic cells.

Polypoid Tumor.—Body of tumor shows smooth muscle largely replaced by fibrous tissue, while the pedicle of the tumor is seen to be infiltrated with cells similar to those described in tumor of the uterine wall.

Ovary.—Shows large follicular cysts and corpora lutea undergoing organization.

Microscopic Diagnosis.—Uterus with fibromyomata invaded by spindle-celled sarcoma; necrosis; hemorrhage; follicular cysts of ovary.

Case 2.—Miss S. A. T. Specimen consists of an irregular mass of tissue composed of uterus and appendages and measures 18 x 13 x 7 cm. At one portion is attached a normal Fallopian tube, which measures 11 cm. in length, and an ovary 1 x 2 x 2½ cm. which has undergone fibrous change. On section the irregular surface of the mass is found to be due to the presence of large, roughly spherical tumors, varying in size from 2 to 11 cm. in diameter. The original form of the uterus can not be made out. The cavity of the uterus is pale and covered with a somewhat sticky secretion. The tumor masses which lie in the myometrium, on section, have the characteristic appearance of myomata; one of the large tumor masses has undergone degeneration, is soft and friable, and contains a considerable amount of blood. Immediately beneath the serous coat are a number of small pedunculated tumor masses which average 1 cm. in diameter. On section these are similar to the large tumor masses.

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Anatomic Diagnosis.—Multiple interstitial and subserous myofibromata of the uterus. Normal Fallopian tube. Fibroid ovary.

Microscopic Description.—In places a definite picture of fibromyoma may be seen. Adjacent to such areas and differentiated from it only by the difference of structure are areas of typical spindle-celled sarcoma. The sarcomatous tissue is extensively necrotic, the necrosis in places being universal, and in other places sparing the cells immediately about the vascular channels. The necrotic areas are infiltrated with leucocytes. Necrosis is seen as well in the myomatous portion, but is not so prominent.

Microscopic Diagnosis.—Fibromyoma invaded by spindle-celled sarcoma.

Case 3.—Mrs. S. E. Specimen consists of about twenty-five separate pieces, which in aggregate make a mass about the size of a man's hand. One large globular mass measuring about 18 cm. in diameter makes up the bulk of the specimen. This mass presents a convex smooth surface covering about three-fifths of the mass. This surface is smooth, pale pink in color, part of surface being glistening and part of it showing firm, blood-stained connective tissue bands. The remaining periphery of this mass is exceedingly irregular and consists of various sized strips of tissue which are soft, friable and deeply stained and show numerous large blood vessels. The contents of many of the blood vessels consist of a firm coagulum. These shaggy strips are distinctly necrotic and are undoubtedly further represented by the numerous small pieces of semi-necrotic material which go to make up the remainder of the specimen. The comparatively smooth surface of this mass is irregularly lobulated and shows beneath the surface a number of small cysts filled with clear amber-colored fluid, also numerous pea-sized to cherry-sized spherical tumor masses, some of which present on cross-section a pearly white glistening surface with a whorl-like arrangement of the tissue elements. On section of the large tumor mass, the cut surface presents a thin cortex varying from 2 to 10 cm. in thickness composed of a firm, pinkish-white tissue beneath which is a whitish, coarsely granular surface showing the remains of numerous small cysts, most of which are filled with a blood-stained fluid. As one gets further away from smooth surface the secton becomes considerably blood stained and takes on a yellowish necrotic look and the cysts become larger in size until finally the semi-necrotic shredded mass described above is reached. The small pieces accompanying this specimen consists of stringy masses of distinctly necrotic tissue similar in character to that described as occurring in the center of the large tumor mass. One of the larger pieces accompanying

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the specimen is thin, averaging about 1 cm. in thickness, and has on its smooth side considerable adipose tissue and resembles in consistency, on cross-section, the firm tissue described as forming the capsule in the main tumor mass. No evidence of tubes and ovaries.

Anatomic Diagnosis.—Degenerated myoma of uterus.

Microscopic Description.—Sections through portion described as capsule of large tumor show thin layer of smooth muscle tissue with invading masses of medium-sized cells having rather darkly staining oval or spindle-shaped nuclei and little protoplasm. Many irregular mitotic figures are seen among these cells. The deeper, softer portions of the tumor are seen to be composed of solid masses of these cells. Numerous thin-walled blood vessels are seen in the cell masses. No evidences of necrosis are seen. Many blood vessels at the periphery of the tumor are completely plugged with the tumor cells. Sections through nodular masses at surface of tumor show smooth muscle tissue rich in cells and a moderate amount of fibrous tissue.

Microscopic Diagnosis.—Myoma of uterus invaded by spindle-celled sarcoma.

Case 4.—Mrs. C. R. Specimen consists of an enlarged uterus measuring 11 x 6 x 5 cm. Peritoneal surface is smooth. The walls are for the most part normal. At one point there is a typical myoma one centimeter in diameter, with a hemorrhagic center. Springing from the mucous membrane are a number of cauliflower-like excrescences over areas varying from 1 to 2 cm. in diameter. These project .5 cm. above the surface of the mucoso, some of them ulcerated, covered by little papillary projections and distinctly hemorrhagic. On section they appear to be part of the new growth which extends down into the uterine musculature. This growth is for the most part distinctly hemorrhagic, though in one or two places of a homogenous white color. In the uterine musculature of the fundus is a small cavity, about a centimeter in diameter, into which projects a number of pinhead-sized, congested, papillary excrescences.

Anatomic Diagnosis.—Adenocarcinoma of the uterus (?). Small interstitial myoma.

Microscopic Description.—Section presents a small piece of typical fibromyoma, at one side of which is a large hemorrhagic mass. The line of separation from blood clot is not distinct. The adjacent portion of tumor shows some lymphocytic infiltration. This hemorrhagic mass shows throughout some necrotic tissue with irregular strands and masses of syncytial tissue composed of cells with a large amount of protoplasm and

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large deeply staining nuclei. The outlines of these cells are not always distinct owing to the fusing of their protoplasm. The syncytial cells are found everywhere in the midst of hemorrhage. The necrotic tissue is moderately infiltrated with leucocytes. The nuclei of the large cells are often irregularly stained, sometimes are so arranged as to give the appearance of giant cells. These masses are in direct continuity with the myoma; in several places a distinct invasion is evident.

Microscopic Diagnosis.—Fibromyoma of the uterus infiltrated with chorio-epitheloma.

Relation to Cancer.—Adenocarcinoma of the fundus was associated with fibroid tumor in six cases; in two of which the fibroid was infiltrated by the carcinomatous tissue.

In five of these cases the uterus was the host of interstitial fibroids of small or medium size. When the relative frequency of adenocarcinoma and squamous cell carcinoma is considered it will be seen that we have here a much higher percentage of adenocarcinoma than is found in the usual run of cancer cases complicated and uncomplicated by fibroids. This agrees with Martin's estimation.

Squamous cell carcinoma of the cervix occurred in two cases. In both cases the fibromata were interstitial and very small.

In view of the relative frequency of adenocarcinoma and fibromata of the uterus, it would seem that the association of the two are worthy of consideration. If the percentage of fibroids at autopsies, 14.8 per cent. (*v. infra*), be taken as an approximate ratio of their occurrence, it seems at least that while the association of squamous carcinoma with fibroids is accidental, the occurrence of adenocarcinoma may be more or less influenced by the presence of fibroid tumors. In this connection statistics compiled from the records of institutions having large series of cases and autopsy reports would be of value.

Complications. — Ovarian cysts occurred in thirteen cases and varied in size from six to twelve cm. in diameter;

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but one was of the papillomatous type. Seven of these cases were additionally complicated by salpingitis.

The two parovarian cysts were of moderate size, about six to eight centimetres in diameter. One tubo-ovarian cyst existed, and was of moderate size.

The ovarian fibromata measured 8x7x4.5 and 20x11x10 centimetres, respectively. The latter was associated with a very small interstitial fibroma of the uterus. Of the two cases of carcinoma of the ovary, one was bilateral, and in both instances the growths were due to metastases from a tumor of the breast.

Cystic ovaries (one or both) in fifty-five cases (twenty per cent.) may seem to be a large percentage, but compares very closely with Scharlieb's[4] estimation of this complication. These are due, it is thought, to the undue thickness or toughness of the ovarian boundaries. There is in almost all these ovaries an increase in the amount of fibrous tissue.

Tubal Complications..—The tubes were diseased in sixty cases; of these thirty-eight were salpingitis alone. In several cases the gross change was slight and the diagnosis made microscopically. In twelve cases there was pus in the appendages in the form of pyosalpinx or tubo-ovarian abscess. There were also eleven cases of hydrosalpinx, of which five were additionally complicated by salpingitis, tubo-ovarian abscess or ectopic pregnancy. One case combines all three—ectopic pregnancy, salpingitis and hydrosalpinx.

It will thus be seen that the ovaries, tubes and adjacent neighborhood were diseased in a large number of cases. Alban Doran states that his experience is more like that of Cullingworth, who found no disease in the appendages save five cases of hydrosalpinx in 100 fibroids. Lawson Tate and Twambly,[20] on the other hand, imply that this condition exists in fifty per cent. of all cases of fibroids. Daniels found disease of the appendages in fifty-eight per cent. of his cases. In this series (including fifty-five cases of cystic ovaries) the

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appendages showed disease in 137 cases, or forty-nine per cent. In addition to these cases there were many cases in which the remains of adhesions were noted, but as it was obviously impossible to estimate this with exactness, without description of the appearance *in situ* at the time of operation this complication has not been noted.

Myomata in Routine Autopsy Work.—On examination the records (Bender Laboratory) of autopsies on women show that fibromyoma of the uterus was found in twenty-six. In two cases apparently death was indirectly caused by the tumor. To what extent the inter-current disease, which was the cause of death in other cases, was hastened in its course by the associated fibroids, can not be deducted. The tumors were large in three (greater than eight centimetres diameter); small in twenty cases (less than four centimetres diameter), of these last ten were single and ten multiple. The age at which these patients died in decennial periods were as follows: Under thirty-five, three; between thirty-five and forty-five, six; between forty-five and fifty-five, six; between fifty-five and sixty-five, six; between sixty-five and seventy-five, four; above seventy-five, one. The youngest was twenty-eight; the eldest seventy-eight. The influence of the tumor was apparent in one case in which death was due to anemia and nephritis; a large submucous tumor by pressure had caused hydroureter and uterine hemorrhages. In a second case a large fibroid tumor of ninety pounds by pressure had caused hydroureter and venous congestion with edema of the lungs. In this case the weight of the woman, less the tumor, was sixty-five pounds. The other cases, which were probably influenced by the fibroid tumor, are deaths from pyonephrosis, pyelitis, rupture of bladder and acute peritonitis. Bishop[21] has collected thirty-seven fatal cases of fibromyomata.

Of the twenty small tumors, one was complicated by tubo-ovarian cyst and hydrosalpinx. Four were associated with adhesions, and one with carcinoma of the ovary secondary to mammary cancer.

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Of the medium sized tumors, of which there were three one was associated with bilateral pyosalpinx which had caused a general peritonitis. The tumors in this case were three in number and interstitial.

The total number of autopsies done on women over twenty years of age, during the seven years in which these autopsy reports were collected, amounted to 175. So that of all adult women coming to autopsy, 14.8 per cent, or one in every seven, had uterine fibroids. From this it may be seen that small fibroids of the uterus may cause little or no disturbance, and that many of these tumors cause no symptoms and are not discoverable during life. The danger of these growths, apart from submucous tumors, is due to their complications, and while these may not always endanger life, it is evident that they frequently cause sufficient disturbance to produce alterations in the surrounding tissues, as is shown by the presence of adhesions, etc.

RELATION OF PATHOLOGIC CHANGES TO TREATMENT.

In conclusion, what deductions can be drawn from this series? So much has been written by men of wider experience that it would be a work of supererogation to add to their well-debated advice. But there are a few questions to be considered:

First, in regard to the advice we must give to a patient suffering from fibroid. It is well understood that the operation for fibroids, in the hands of capable operators, is in uncomplicated cases practically devoid of danger. It is to complications and degenerations that mortality in fibroid tumors is due, as we know from experience and from published reports. Delay in an uncomplicated fibroid exposes the patient to the possibility of the development of complications. And with the large percentage of complications in this series it is evident that with delay the liability to complication is increased. While this is so, it is evident that there is one class of fibroids which may cause few or no

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symptoms, viz., the small subserous and interstitial tumors. We may, therefore, say that delay is justifiable only in these latter cases and not justifiable in even these when complications exist.

In reference to the extent of operation, while it is obvious that myomectomy is the ideal operation, there is no doubt that it is only applicable to a small class of cases—those in which the tumors are easily accessible and in which it is possible to eradicate them completely. If eradication is not complete, there is the possibility of renewed growth, and should pregnancy occur, with its increased blood supply, this possibility is the greater. This should be kept in mind, as those cases in which myomectomy is desirable are usually childless women.

It is at present accepted that the operation of supravaginal hysteromyomectomy[22] is accompanied by the lowest mortality[23]. But this operation is obviously not applicable to those cases with malignant degeneration and associated with malignant disease of the uterus. Such cases demand complete extirpation of the cervix. Should, however, the commonly accepted operation of supravaginal hysteromyomectomy be attempted, and on opening the uterus adenocarcinoma or suspicious necrotic change be seen, the cervix may be removed and a complete ablation done.[24]

Adenocarcinoma and sarcoma are the forms of malignancy which, in connection with fibroids, are most likely to come to operation unrecognized. If, however, the case be uncomplicated by malignancy, the choice must lie between amputation through the cervix and myomectomy. It is rarely advisable to do myomectomy when the appendages are adherent or in the presence of old or recent infection. The site of enucleation may become the starting point of a peritonitis.[25] In view of the large percentage (21.4) of diseased tubes, it is evident that myomectomy is limited to a small class of cases.

Should amputation through the cervix be the operation of

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choice, one or both ovaries may be left to ameliorate the symptoms of the surgical menopause. In such cases not only must the question of infection from the tubes be considered, but also the condition of the ovary. In a large percentage of this series cystic ovaries were found. A cystic ovary should not be left; if necessary, resection may be done and the cysts removed.

CONCLUSIONS

First. Fibroids which are producing symptoms, and all fibroids except those designated as small (especially when subserous or intramural), should be removed, because the risk to the patient from operation is far less than that from the tumors themselves.

Second. In view of the sarcomatous changes, carcinomatous associations and complications of uterine fibromyomata, early removal is indicated when they are of sufficient size to produce symptoms. Small uncomplicated tumors not producing symptoms do not require early treatment.

Third. Thorough pathologic examination should be made of all fibroids for evidence of malignancy. Particular study should be devoted to those tumors which are necrotic, cystic or both, as among these are found the largest proportion of malignant changes.

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Reprinted from the ALBANY MEDICAL ANNALS, July, 1904

A PECULIAR HYPERTROPHY OF THE PROSTATE, ACCOMPANIED BY AN ASCENDING INFECTION AND CYSTS IN THE URETERS, WITH A GENERAL DISCUSSION OF URETERITIS CYSTICA.

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While hypertrophy of the prostate is of common occurrence, the peculiar form to be described is unusual and explains some of the difficulties of catheterization and cystoscopic examination met with in this condition. The formation of cysts in the mucous membrane of the ureter is, on the other hand, much less frequent, being noted but twice in the records of over 600 post-mortem examinations at the Bender Laboratory. Previous to 1894 Lubarsch[1] cites but ten cases in the literature and found the condition himself in four out of 3,000 sections.

Following is a brief summary of the two cases we wish to report:

CASE I.—(Bender Laboratory Records, autopsy No. 0-604). *Clinical History:* E. S., male, age 80, admitted to the Albany County Hospital, February 18, 1903. Patient complains of diarrhœa and difficulty in voiding his urine. Family history—negative. Past history—Has used alcohol

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freely. Denies any venereal infection. Present condition—The patient's mental condition is defective and he gives untrustworthy replies to questions relating to his illness. He has used a metal catheter for some time, passing it himself without antiseptic precautions.

Physical Examination—The heart, lungs and abdomen negative. The rectum is prolapsed. The left testicle is apparently swollen, tense and transmits light and is about 8 centimetres in diameter. The prostate per rectum is found to be enlarged. There is a purulent discharge from the urethra. When the urine is withdrawn by a rubber catheter the first portion is pure pus and is followed by ammoniacal cloudy urine. Death ten days after admission, February 28, 1904.

Autopsy seventy-two hours after death by Dr. A. T. Laird.

Anatomical diagnosis.—Hypertrophy (fibro-myoma) of the prostate. Diphtheritic cystitis. Ascending infection (pyelo-nephritis) of both kidneys. Bilateral ureteritis cystica. Acute vesiculitis. Chronic interstitial nephritis. Chronic interstitial orchitis. Tuberculosis of epididymis and prostate.

Prostate—Shows hypertrophy, particularly in the lateral lobes, which cause obstruction to the outflow of urine, not, however, by pressure upwards as is seen with hypertrophy of the middle lobe, but rather by pressure downward. The chief hypertrophy is in the right lateral lobe, which extends across the upper wall of the urethra. It is peculiar in being attached to the lower portion of the gland by a thin pedicle which allows considerable mobility of the tumor. Extending outward in a lateral direction from the prostatic portion of the urethra is a pocket which measures 3 x 2 centimetres and which communicates with the bladder by a narrow orifice. Into this pocket the pedunculated lateral lobe fits, completely closing the communication between the bladder and the pocket, thus preventing the passage of urine and acting as a "drop latch." When a catheter is introduced it passes into the pocket and drains the pus which has accumulated there, at the same time it lifts the pedunculated lateral lobe allowing the urine to escape. The mucosa lining the pocket has a greenish grey color and is studded with fine miliary abscesses. The left lobe of the prostate is firm in consistency; the right lobe is softer than normal and nodular and on section the stroma predominates; small yellowish areas of glandular tissue are present. In the left lobe no glandular tissue can be found.

The Bladder is externally roughened and congested and attached to the adjacent coils of the small intestines by fresh adhesions. There are also extensive adhesions between the rectum and bladder. The bladder is dilated, its walls average 0.5 centimetre in thickness and it is infiltrated with pus throughout all its coats. The mucosa is covered with a seropurulent exudate and is of greenish color with here and there streaks of red.

The Right Kidney—Measures 9 x 5 x 3 centimetres. The capsule strips readily leaving a smooth surface. Beneath this are found a number of minute yellowish areas about 0.5 centimetre in diameter, which when

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sectioned appear to be made up of purulent material. The substance of the kidney appears normal, although the markings are somewhat indistinct. The pelvis of the kidney is dilated and the mucosa is congested.

Right Ureter—The mucosa is congested and about fifty small cysts project from it into the lumen. They have a glistening yellowish color and are filled with serous fluid which is under considerable pressure, spurting out when the cysts are punctured. In some cysts the contents are slightly tinged with blood.

The Left Kidney—Measures 7 x 4 x 3 centimetres. It has been converted into an abscess cavity and but very little of the normal kidney substance remains. The abscess cavity is lined by a purulent membrane. The mucosa of the pelvis is swollen and is covered with a purulent exudate.

Left Ureter—Is much dilated, measuring 1.5 centimetres in diameter. About a half centimeter from the ureteral orifice in the bladder several cysts are found, smaller, however, than in the ureter of the opposite side.

Seminal vesicles—Contain pus and yellow mucoid material.

Right testicle—Shows extensive atrophy. There is also a hydrocele measuring 10 x 4 centimetres.

Left testicle—The globus major of the epididymis is caseous and the interstitial tissue of the testicle is increased.

Urethra—Stricture of large calibre in the bulbous portion.

Histological Description—The cysts of the ureter are surrounded by a distinct membrana propria derived from the submucosa and are lined by transitional epithelium. The cyst cavities are filled with exudate often hemorrhagic, and containing desquamated epithelial cells. Among these are oval, pale, faintly staining bodies frequently showing nuclear shadows. The epithelium of the ureter is absent for the most part over the cysts; only a few strands of connective tissue separating the cysts from the lumen. Several of v. Brunn's cell nests are present in the submucosa; no lumen connecting them with the ureter can be found.

Microscopic examination of the cyst contents showed many epithelial and pus cells and bacteria. Peculiar round or oval highly refractive bodies containing vacuoles are also present and with Sudan III give the characteristic reaction for fat. Cultures made from the cysts showed the presence of the B. coli communis.

CASE II—(Bender Laboratory Records, Autopsy No. 0-323). L. G. R., female, aged 54. Autopsy, October 20, 1900, by Dr. G. Blumer.

Anatomical Diagnosis—Left renal calculus. Right ureteral calculus. Pyelitis on right side with atrophy of kidney. Cystic ureteritis. Pyelonephrosis with multiple miliary abscesses of kidney substance. Cystitis. Brown atrophy of heart muscle. Emphysema of lungs with hypostatic congestion and œdema. Cloudy swelling of the liver. Acute splenic tumor.

Left Kidney is greatly dilated and on section the pelvis is found to be enormously distended with thick greenish pus and contains a single yel-

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lowish white stone, granular in appearance (phosphatic). From it at one point a brownish stone projects, probably uratic (?) in origin. The removal of the capsule tears away the kidney substance which moreover is greatly diminished in amount. The surface of the kidney is congested and dotted with miliary abscesses.

Left ureter is markedly dilated and the mucosa is covered with little polypoid excrescences, perfectly round and translucent and average 1 centimeter in diameter.

Right kidney is greatly contracted and on removal of the capsule the surface is finely granular. On section the cortex is considerably diminished in amount. The pelvis of the kidney is dilated and contains thick pus.

Right ureter is blocked about 2 to 3 centimetres above its vesical orifice by several small stones.

Bladder contains thick muco-pus greenish in color. It is markedly contracted and the mucosa is congested.

Bacterioscopic—In the kidney abscesses was found a bacillus of the mucosus capsulatus group.

Histological Examination of cysts in the ureters. The cysts are located in the submucosa but project prominently into the lumen of the ureter, fully five-sixths of the cysts are above the level of the mucosa. The epithelium of the ureter has desquamated over the cysts leaving only a few strands of connective tissue. This connective tissue, derived from the submucosa, surrounds the cysts and also separates them from the lumen of the ureter. The lining of the cysts is composed of epithelium similar to that lining the ureter, that is transitional epithelium. At the base of the cyst are several layers of epithelial cells, but at the periphery where the pressure is greatest there are fewer layers and the cells are quite flattened. The contents of the cysts are in some cases colloid material similar to that found in the thyroid; in others, cellular debris. In the contents oval and refractive bodies, three to ten times the size of a leucocyte, are constantly present and in some of these faint bodies can be seen (nuclei). These are probably identical with the so-called sporozoa that have been described in association with cysts of the ureter.

Several of v. Brunn's cell nests are present in the submucosa. In one instance a connection between a nest and the lumen of the ureter exists.

Formation of Ureteral Cysts

Cysts of the ureter, pelvis of the kidney and bladder were first described by Rayer[3] and later by Rokitansky[3] and Morgagni[4]. Virchow[5] thought their formation in the ureter was due to a blocking of the crypts in the mucosa of the ureter followed by a retention of secretion; and in the bladder, on account of the presence of concentric bodies in the

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To Illustrate Dr. Carey's and Dr. Laird's Article on "A Peculiar Hypertrophy of the Prostate."

Albany Medical Annals, July, 1904.

Fig. I —Shows the cysts in the mucosa of the ureter (actual size).

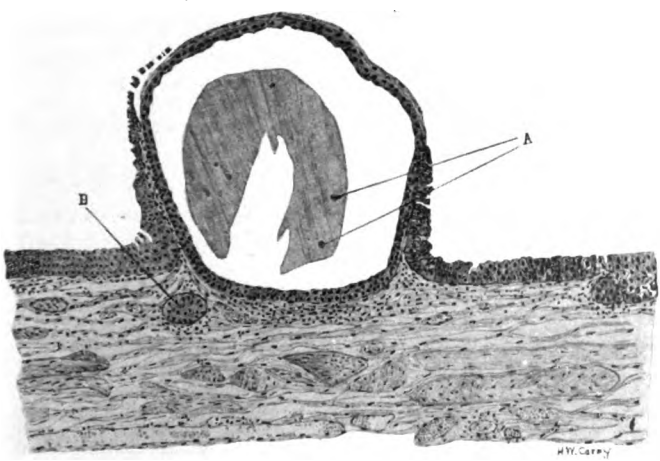

Fig. II.—Shows the structure of one of the cysts; the membrana propria extending entirely around the cyst wall. (A) are the bodies described as degenerated epithelial cells (so-called sporozoa); (B) a cell nest (v. Brunn); (objective, 1-6; ocular, I.).

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cyst contents, attributed them to misplaced prostatic glands. Hamburger[6] described glands in the mucosa of the ureter which simulated the appearance of sebaceous glands and he thought the cysts originated from these. In a histological study of the ureter v. Brunn found nests of epithelial cells surrounded by a membrana propria and called attention for the first time to the peculiar arrangement of the connective tissue beneath the epithelium of the ureter. This arrangement is that of a meshwork with thickening at the nodal points forming septa which extend upward into the epithelial layers. The height of the septa varies inversely with the intra-ureteral pressure, being higher when the pressure is low. To variations in pressure v. Brunn[7] attributed the formation of these cell nests, small portions of the epithelium being enclosed and surrounded by the septa of connective tissue.

To determine whether cell nests were normally present Aschoff[8] studied the pelvis of the kidney, the ureters and the bladder in the new born and adult, but in no instance were they present, hence they are not constant elements. He discredits the influence of pressure in the formation of the cell nests.

Later investigations of Lubarsch[9], Marckwald[10], Stoerk[11], Zuckerhandl[12] and Paschkis[13] support the theory that the cysts originate from the cell nests of v. Brunn.

The method of formation of the cysts is described by Aschoff as follows:

(a) Enclosure of a portion of epithelium by septa of connective tissue with the formation of a cell nest. This causes small macroscopic nodules or granules in the mucosa of the ureter.

(b) Central degeneration of these cells accompanied by a transudation of fluid into cysts cavity.

The Location of Cysts is fairly constant and corresponds to the points of constriction in the ureter. They are almost constantly found in the pelvis of the kidney, upper third of the ureter and at the uretero-vesical orifice on the trigonum. They are frequently bilateral. In the two cases above reported the distribution of the cysts was diffuse and not limited to any portion of the ureter.

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Etiology.—The exact cause of the formation of these cysts in the ureter is not known, but in the large majority of the cases reported they developed in association with inflammatory and suppurative conditions of the bladder, ureter and pelvis of the kidney (ascending infections).

In the twenty-four cases, including our two, a cystitis, calculus or pyelitis existed in all but two; in the latter no lesion of the urinary tract could be found.

Mention has been made above of the oval translucent bodies found in the cysts contents. These have been described as sporozoa by v. Kahlden[14], Pisenti[15], Silcock[16], Eve[17], Clark[18] and Sutton[19], and were believed to be the cause of the cyst formation. This view has not been supported by later investigations since the parasites could not be cultivated from the cysts and moreover it is improbable that any infection of this nature should always be limited to such a prescribed portion of the urinary tract.

The so-called sporozoa in our sections, while resembling parasites in some respects, were by no means constantly present in the cysts and never very numerous. They were never found outside of the cysts, in the lumen of the ureter or in the epithelium; where they were surrounded by cellular debris a gradual transition from epithelial cells to these so-called parasites could be traced. In some, several faint nuclei could be seen. It is our opinion that these parasitic like structures are an early stage in the degeneration of the epithelial cells lining the cysts and later become colloid. The interest in this condition of Ureteritis Cystica does not, however, relate entirely to its pathology. Aschoff has called attention to the fact that in the early stages of the formation of the cysts they may be mistaken for miliary tubercles in cystoscopic examinations.

In one of the cases reported by Marckwald the development of the cysts had been so extensive as to block the ureter completely, giving rise to great hydronephrosis. Healton and Gamgee[20] have reported a case in which haematuria had existed for many years and at autopsy a cystic villous papilloma of the renal pelvis was found. The bleeding, in part, was due to the rupture of the cysts.

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Resumé

1. Hypertrophic lateral lobes of the prostate may be pedunculated and by their downward pressure on the urethra obstruct the outflow of urine, acting like a "drop latch."

2. The origin of cysts in the ureter is attributed to the central degeneration and later transudation of fluid into v. Brunn's cell nests.

3. Ascending infection of the urinary tract is the important factor in the etiology of these cysts.

4. The peculiar translucent oval bodies resembling sporozoa are in some instances the product of epithelial degeneration.

5. The cysts may, in their early stages, simulate miliary tubercles.

6. Cysts of the ureter may cause obstruction to the passage of urine from the kidney to the bladder with consequent hydronephrosis.

7. Rupture of the cysts can give rise to haematuria.

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Reprinted from the ALBANY MEDICAL ANNALS, August, 1904

INFANTILE INGUINAL HERNIA OF THE VERMIFORM APPENDIX WITH ADHESION TO THE EPIDIDYMIS.*

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Hernia of the appendix is not rare, but it is uncommon. Morgagni, in 1750, was, perhaps, the first to make reference to it. Scarpa reported several cases in 1806, after which we have series of cases reported by Klein, Brieger, Bajardi, Rivet, Gibbon, and others, until, in 1899, Peterson was able to collect 116 published cases, while Piersol, in 1901, estimated the number of reported cases as 125. That it is more frequent than the number of reported cases would lead one to believe appears from the fact that Coley found hernia of the appendix, without the presence of other portions of the intestinal tract, five times in 351 operations for femoral or inguinal hernia.

Hutchinson classifies hernia of the appendix into two divisions, congenital and acquired. The congenital form is always inguinal, and almost invariably occurs in the male sex and on the right side. In this form it is the rule to find adhesions between the appendix and some of the remains of the processus vaginalis—either to the wall of the sac, the cord or to the tunica vaginalis. The origin and significance of these adhesions have been the subject of much speculation. They have been ascribed to the persistence of folds of peritoneum normally present in fœtal life; or as the result of

* Previously published in briefer form in the *Archives of Pediatrics* (March, 1904) to which journal we are indebted for the use of the accompanying cut.

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fœtal peritonitis, the frequency of which is upheld by Virchow, B. Schmidt, Orth and others; to the persistence of certain fibres of the gubernaculum; and they have also been considered as of post-hernial origin. There seems to be little doubt that in some of the cases these adhesions, by uniting the appendix to the migrating structures, have enabled the same forces which bring about the descent of the testicle to also play an active part in causing the descent of the appendix into the inguinal canal.

In support of the view that these attachments may originate in fœtal folds of the peritoneum may be cited the fact that previous to the descent of the testicle into the inguinal canal the peritoneum overlying the testicle encloses it and forms a mesentery, the mesorchium, which also encloses the gubernaculum and forms two folds, one above the testicle and the other below it. The one below the testicle encloses the lower part of th gubernaculum, and is known as the *plica gubernatrix;* the one above the testicle is not constant, but when present usually covers the spermatic vessels and is known as the *plica vascularis.* Hutchinson states that at the time the testicle passes into the inguinal canal this ascending band or ridge of peritoneum can be found in about ten per cent. of all cases: its upper attachment varies; usually it is to the under surface of the mesentery of the lower end of the ilium, less commonly to the cæcum or vermiform appendix. A similar band is much more frequently found in females (fifty per cent. of all cases, according to Hutchinson), in whom it persists as the well-known appendiculo-ovarian ligament. The presence of this band with rigid superior attachments has been given as a cause of incomplete descent of the testicle.

As is well known, the testicle develops opposite the second or third lumbar vertebra, from which point it descends during the third month, by the end of which time it has reached the internal ring. It remains in this position until near the close of gestation or, according to some authors, enters the processus vaginalis as early as the middle of the seventh month. The position of the appendix is high in the abnominal cavity until the descent of the cæcum, which occurs about the sixth month, but, owing to the relatively great length of the appendix in the fœtus (eleven millimetres in each of two twelve centimetres fœtuses examined by us), it is at all times capable of coming in contact with the peritoneum covering the testicle. It is thus seen that inflammatory

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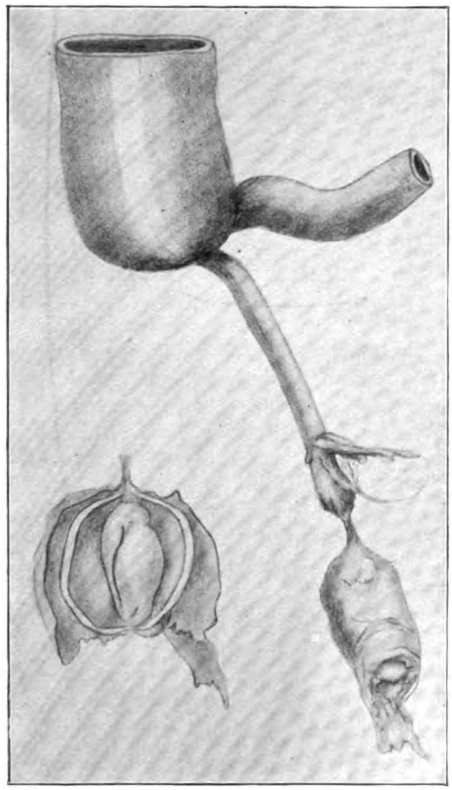
To Illustrate the Article by Drs. Stanton and Shaw on "Infantile Inguinal Hernia of the Vermiform Appendix."

Albany Medical Annals, August, 1904.



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conditions occurring in either the appendix or the testicle could result in the formation of adhesions between the appendix and the migratory peritoneum covering the testicle, and thus cause the descent of the appendix along with the testicle.

The following case, occurring in the service of one of us (Shaw) at the Albany Orphan Asylum, is of interest in that it represents a case of congenital hernia of the appendix, in which the descent of the appendix into the inguinal canal was undoubtedly caused by an early inflammation which involved both testicles, together with their peritoneal covering, and which resulted, we believe, in the formation of an adhesion between the distal end of the appendix and the tunica albuginea overlying the head of the right epididymis.

Sidney P., born November 10, 1902; admitted to the Albany Orphan Asylum January 31, 1903; died October 29, 1903. While under observation in the Asylum there were no symptoms referable to the appendix or genital organs; the patient dying of broncho-pneumonia following measles.

The following notes are from the autopsy protocol (Stanton):—

Abdomen—Abdomen is free from fluid. Omentum contains very little adipose tissue. Serosa smooth and glistening. Appendix is eight centimetres long and extends directly downward with free meso-appendix from caecum through internal ring and inguinal canal and is so united by adhesions to the testicle that the latter can be drawn up into the inguinal canal by traction on the appendix.

When the testicle is in normal position there is a slight evagination of the peritoneum around the appendix at the right of the internal ring; otherwise the funicular process is completely obliterated and there is no evidence of a hernia sac.

On dissecting out the appendix it is found that the portion lying within the canal is covered with a loose areolar tissue while a thick band of firm fibrous tissue unites the tip of the appendix to the tunica albuginea overlying the head of the epididymis.

Testicles—The parietal and visceral layers of the tunica vaginalis of both testes are distinctly thickened.

Anatomical diagnosis—Bilateral broncho-pneumonia. Cloudy swelling of liver and kidney. Acute congestion of spleen. Congenital hernia of appendix with adhesions between epididymis and appendix. Chronic bilateral peri-orchitis.

Microscopic examination—Sections from the left testicle show extensive thickening of the capsule and a growth of fibrous tissue between the tubules.

Microscopic diagnosis—Broncho-pneumonia; endothelial hyperplasia in spleen and retroperitoneal hemolymph node. Albuminous and fatty degen-

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eration of liver. Slight albuminous degeneration of kidney. Atrophied thymus. Cloudy swelling of heart muscle. Chronic orchitis. Chronic periorchitis.

Explanation of illustration—The larger drawing shows the parietal peritoneum becoming continuous with the peritoneum of the appendix at the point where the appendix entered the inguinal canal and the band of fibrous tissue uniting the tip of the appendix with the tunica vaginalis. The smaller drawing is from a section through the tunica vaginalis showing the thickening of the parietal portion and the relation of the adhesion to the tunica vaginalis and the head of the epididymis.

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Reprinted from ALBANY MEDICAL ANNALS, January, 1904.

A STUDY OF THE CHANGES OCCURRING IN THE ENDOMETRIUM DURING THE MENSTRUAL CYCLE.

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(*From the Bender Laboratory, Albany, N. Y.*)

Probably the first recorded observations on the condition of the uterine mucosa during menstruation were published by Kundrat and Engelmann in 1873. Since that time numerous investigators have studied the subject but the results of their work show the greatest differences of opinion.

Without doubt, as we shall see, these varied views were due to several causes, principally the source of the material and the more accurate results obtained through better preserving fluids and more satisfactory fixing methods as well as to the recent rapid progress in microscopical studies.

In the study of the changes which take place in the uterine mucosa during the menstrual cycle we have several methods to pursue. The first method employed was that of the examination of the mucosa in uteri removed at autopsy and consequently, as this was the most natural source for the securing of material for microscopical study, we find that the earlier and the greater number of observers, Kundrat, Englemann, Sir John Williams, Sinety, Leopold, Wyder, Von Kohlden, Christ, and Wendeln conducted their studies on the uteri removed at autopsy from patients who had died during menstruation.

That the earlier observations were faulty is not to be wondered at since it is a well-known fact that autopsy material unless secured very early post mortem is more or less changed. Gebhard referring to the conclusion of Wendeln obtained by the study of autopsy specimens, claimed that it is never allowable to show cadaveric preparations as proof of the condition of the mucosa where the material has been taken thirty-four hours post mortem. We believe that even this is rather late to secure proper material.

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In the first place, as pointed out particularly by Leopold and Wyder, it is absolutely necessary that an exact anamnesis be secured in each case, whatever the source of the material, in order to be assured that one is dealing with a true menstrual hemorrhage. That this has not been followed in many of the earlier observations is certain.

Another source of error in the earlier observations, and one that is liable to be experienced by every laboratory worker unless the greatest care is taken, is that in passing the material through the fixing solutions there may be more or less loss of substance. Inasmuch as the first important question to be decided is whether there is a loss of substance resulting from menstruation or not, it is necessarily important to use such fixing solutions as will preserve the specimens intact.

A number of authors have not stated their methods of preserving and fixing their material. A number employed Müller's fluid. Leopold preserved his specimens first in weak then in stronger alcohol. He was opposed to Müller's fluid because the superficial layers which are saturated with blood are easily broken off. This is certainly true unless the specimens are most carefully handled, and it is due to the fact that Müller's fluid must be changed and the specimens washed so often before the tissue is fixed. After hardening has taken place the pieces of tissue may then be moved about and the fluids changed frequently without loss of substance. Mandl finds that the corrosive sublimate solution proves the best for the study of the condition of the epithelium and that Flemming's fluid was of the greatest service for the study of the process of regeneration.

Finley and other recent observers used Zenker's solution and since this fixes the specimens quickly without changing the solution and without handling them frequently it has proved very satisfactory. Could this solution have been used in earlier observations there would have been less disagreement as to the changes which take place especially as regards the loss of substance.

Möricke was the first to examine scrapings from the normal menstruating uterus and thus excluded the possibility of post-mortem changes. Lëhlein, Gebhard, Westphalen and others soon followed his example and these investigators arrived at different conclusions than did the earlier observers who used autopsy material. Wendeln had some doubt of the value of the examination of curettage specimens on the grounds that the whole mucous

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membrane is not obtainable and consequently conclusions based on the examination of only a part should not be made. It is possible, too, that curetted material may appear hemorrhagic on account of the numerous blood cells which are intimately associated with the material in its removal and in the process of blocking.

Sinety examined the menstrual flow and the mucus adhering to the superficial layer of the mucosa in order to draw conclusions as to the condition of the deeper layers. In such a method the possibility of arriving at erroneous conclusions is apparent. Wyder aspirated the menstrual discharge from the cavity of the uterus by means of a uterine syringe in order to avoid the glands of the cervix and to reduce the negative pressure to a minimum.

In order to determine the probable loss of substance of the mucosa during menstruation the writer undertook to examine the napkins of thirty patients through the menstrual period. The patients were instructed to change the napkins frequently and to soak in cold water, being careful to save any clots and at the end of menstruation to take a vaginal douche of plain cold sterile water so that all the discharge might be collected. This douche water and that in which the napkins were soaked was centrifuged so as to obtain all the sediment possible. This sediment was then hardened in alcohol and passed through in the routine manner. Great care was taken to secure patients who had a normal menstrual history and in whom there was no apparent diseased condition of the endometrium.

The small amount of material thus obtained was cut and stained with hæmatoxylin and eosin. The result of such examination will be mentioned later on.

Another method which is the most important of all is that of the examination of sections of uteri removed during the menstrual period for lesions not involving the endometrium. This method of examination was only lately carried out since surgeons prefer not to remove the uterus during active menstruation.

Probably the most elaborate investigations were carried on by Gebhard, in Berlin, and Westphalen, in Keil, who not only studied the mucosa of menstruating uteri obtained by curettment and of uteri obtained at autopsy but also sections of uteri removed by operation during the menstrual period. Williams, Findley, Edgar and others in this country also recorded their observations on the examination of the mucosa of uteri removed during operation.

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In women, who must lose diseased adnexia and in whom the anamnese and the examination of the uterus led one to expect no particularly abnormal condition of the uterine mucous membrane, Mandl and other operators awaited menstruation and removed the uteri during this period. No intra-uterine manipulation was carried out and in order to protect the organ from unnecessary handling extirpation was performed as quickly as possible by clamping off the parametrium and ligaments and cutting rapidly. In order to avoid the slightest possible injury to the mucosa the uterus was opened on the anterior wall cutting from the cervix to the fundus and then a portion was removed from the posterior wall and placed immediately in fixing fluids. Findley placed the uterus in salt solution immediately after removal and then placed in Zenker's solution for twenty-four hours.

The views of the numerous investigators are so contradictory on several points that it will be necessary to consider them more in detail.

Leopold divides the menstrual cycle into four stages: (1) active menstruation; (2) regeneration; (3) resting stage; (4) premenstrual swelling.

In as much as the stage last mentioned is really the preparatory one, according to my observations, and the beginning of the phenomena exhibited in the change of the uterine mucosa due to menstruation, we will discuss this division of our topic first.

Westphalen, Leopold, Doléris, Pompe, Van Meerderwordt, Herzog, and others are practically agreed with the conclusions of Gebhard based on his observations of the scrapings and sections of uteri removed during the menstrual period for lesions not involving the endometrium.

From a study of the literature on the subject, and from the examination of such material as I have been able to secure, the following information has been gleaned.

In this stage, which begins to develop gradually as soon as the process of regeneration is complete, which is about the eighteenth day after the flow ceases, we find that the capillaries of the mucosa are congested resulting in a serous or serosanguineous exudate infiltrating the stroma of the mucosa. During the state of regeneration the cells of the stroma lay over each other rather thickly but now become pressed apart particularly in the outer third of the mucosa.

The protoplasm of these cells become compressed and the pro-

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jections by which they are bound together are either greatly lengthened or completely separated. In the meshes lies a light opaque mass, which seems similar to blood serum and which is often separated in the larger vessels from the chromocytes.

Later the blood leaves the capillaries and infiltrates the stroma, gravitating in the direction of least resistance, *i. e.*, toward the uterine cavity, and, just before the active flow begins, forming a collection of blood beneath the surface epithelium—the sub-epithelial hæmatoma of Gebhard.

It is quite impossible to say whether the bloody condition of the effusion along the borders of the mucosa belongs entirely to the normal or not, for it is apparent that in curettage hemorrhage easily occurs in the mucosa while in extirpation an engorgement of the vessels occurs very easily, especially when the broad ligament is not clamped. Even traction on the uterus from below, according to Westphalen, results in venous stasis with consequent small hemorrhages.

The vessels become larger in the loosened swollen stroma and are for the most part more filled than in the period of regeneration but the greater increase in size occurs only shortly before the beginning of menstruation proper.

Many observers agree that there is also an increase in the size of the glands of the mucous membrane, since these appear widened and winding and frequently on cross section the walls seem to be thrown into folds in the lumen. The increase in size of the glands is due, no doubt, to the collection of the secretion of the gland cells. It is this mucous-like product of the gland cells which gives them quite a granular appearance. The gland cells become uniformly swollen and take stains more evenly, and their nuclei are more widely separated as a result of the increase in the volume of the protoplasm, and are uniformly more round in comparison to the oval-nuclei which are seen in the regeneration period. In all the stages the cell nuclei are near the base as a rule, although Westphalen has often noticed that they stand in the middle of the cell in the beginning of the state of pre-menstrual swelling. Consequently the mucosa is increased in thickness from two to three millimetres up to six and seven millimetres,—the thickness varying greatly in the same uterus owing to the unequal distribution of the muscle layers directly beneath the mucosa.

Kundrat and Englemann found a fatty degeneration of the mucous epithelium as well as of the gland cells and interglandular

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tissue and the hemorrhage and œdema of the mucosa according to these early investigators, were produced by a fatty degeneration of the walls of the vessels which were now increased in size and completely filled with blood—these conditions resulting in a laceration of their walls and a consequent hemorrhage into the tissue. They noticed that the greater part of the hemorrhage was superficial and that fatty degeneration is most noticeable in the same portion of the mucosa.

Sir John Williams also believed that fatty degeneration occurred and consequent degenerative changes took place.

Leopold claimed, and rightly, that the hemorrhage is a superficial capillary one due largely to the peculiar condition of the vascular structure in the mucosa (numerous arteries and capillaries and proportionally a less number of veins). What he described as a fatty degeneration of the superficial elements, was assigned, not as the previously mentioned observers assigned as the cause, but as the result of the hemorrhage.

Möricke and other observers maintain that fatty degeneration of even the slightest grades is not to be found.

Kundrat, Sinety, Leopold, and others have described an increase of the round cells and small celled infiltration but this is not confirmed by subsequent observers and their presence is denied by others.

Leopold described the appearance of giant cells (with eight to ten and even more nuclei) especially in the projections of the mucosa into the muscular tissue. Other investigators have confirmed this observation.

At the end of the pre-menstrual stage we find, therefore, the mucosa is swollen greatly and infiltrated with a serous or serosanguineous exudate and that collections of blood are formed beneath the surface epithelium ready to burst out.

The stage of active hemorrhage now appears—being described as the first stage by Leopold and as the second by Gebhard. The question now arises as to how the blood reaches the uterine cavity and how much mucous tissue is destroyed by this process.

Gebhard states that the blood reaches the uterine cavity by being forced between the epithelial cells of the surface or of the glands, or the continuity of the surface is broken by the lifting of small masses of cells from their bed these providing an exit for the collections of blood beneath.

Christ believed that in the weaker menstrual congestion the

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To Illustrate Dr Lipes' Article on "A Study of the Changes Occurring in the Endometrium during the Menstrual Cycle"

Albany Medical Annals, January, 1901.

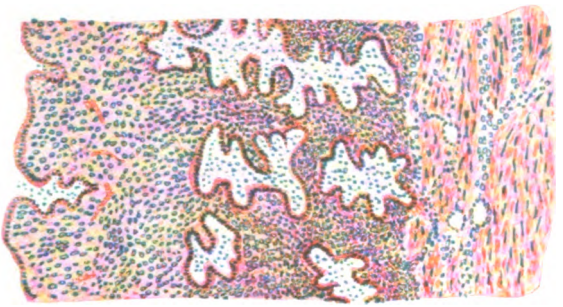

FIGURE 1

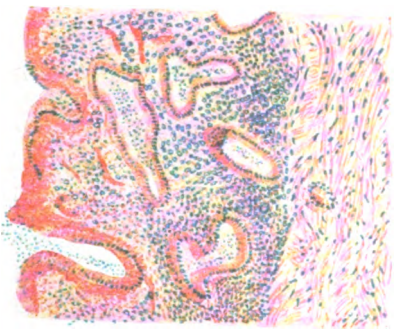

FIGURE 2.

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blood escaped between the epithelial cells of the surface of the mucosa and of the glands. Where the congestion was more marked slight defects occurred in the surface through which the blood poured out and where the menstrual flow was very profuse there was a more sudden and a greater loss of the surface epithelium, which allowed the outflow of blood. This observer claimed to have seen in many places the passage of red cells between the superficial epithelium as well as between the epithelium of the glands but he has given us no drawings of this condition. Others agree with this view but do not make the statement as a result of their own observations.

Mandl made careful examinations of a number of sections but did not observe in any case the passage of red blood cells between the epithelium although these cells are easily observed when specimens are fixed in sublimate solution and stained in hæmotoxylin and eosin—the method is adapted. He repeatedly found leucocytes, however, which had become fixed in their wanderings between the epithelium of the surface and of the glands as well, and believed that by the wandering of these leucocytes the union of the epithelial cells is broken so that the blood follows more easily in such places.

But perhaps the most important question, and the one concerning which there is the greatest diversity of opinion, is whether or not any portion of the mucosa is destroyed by the process of menstruation.

If we examine the results of the studies of the various authors already mentioned we will see that the earlier observers particularly held the opinion that not only is the whole superficial epithelial layer destroyed but also a considerable part of the mucosa disappears.

Another group of observers believe that the whole mucosa and even the superficial epithelial layer remains intact; while a third group takes the middle ground and describes a loss sometimes of a less, sometimes of a greater part of the epithelium and mucous membrane.

In the first group we find Engelmann, Kundrat, Sir John Williams and Von Kahlden. The latter, who undertook a through study of the published communications on this subject up to the appearance of his work in 1889, came to the conclusion that in all probability in menstruation the whole surface epithelium with a very considerable part of the mucosa is thrown off. But these

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observations were made on cadaveric material which had been obtained when post-mortem changes had probably taken place and the fixing solutions used necessitated frequent changes and consequently much handling. As already pointed out these conditions would result in a loss of substance in such frail material as the uterine mucous membrane, especially during menstruation.

Of the group of men who believe that at no time during menstruation is any part of the mucosa lost, De Sinety is the only early worker on autopsy material. Möricke, Strassmann, Findley, J. Whitbridge Williams, C. Ruge, Veit, Gebhard, Mandl, Leopold, J. Clarence Webster, Meerdervoort and others believe that only a small portion of the superficial epithelium is lost and that this is purely accidental.

Underhill, Wendeler, Heape, and others, believe that only the superficial portion of the mucosa is destroyed.

There is no doubt but that the character of the hemorrhage has much to do with the amount of destruction of the superficial epithelium. If the congestion is of rapid development and the collection of blood beneath the surface epithelium is extensive there must necessarily follow a destruction of at least a portion of the overlying surface epithelium. If the hemorrhage is slight and takes place largely by diapedesis the loss in the epithelium would be almost nil.

This I have proved, at least to my own satisfaction, by the examination of the menstrual discharges as already mentioned. Lack of space will not allow a detailed description of these cases.

In the thirty cases examined the period of menstruation extended from one to eight days. There were two cases of one day's duration, one of two days, twelve of three days, seven of four days, three of five days, two of six days, two of seven days, and one of eight days' duration, all of which were carefully examined.

In the first three cases mentioned there was practically no sediment and this was composed principally of red-blood cells and some vaginal epithelium. In two of the twelve cases where the flow lasted three days the onset was severe and the flow considerable, but with little or no pain experienced by the patient. In these two cases there was considerable sediment which contained a large amount of blood and numerous epithlial cells from the mucosa, as well as vaginal epithelium and other debris.

In one of the seven cases menstruating four days, the flow was

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slight the first day but increased in severity the last three days. In this case, however, there were not many epithelial cells found in the discharge. In the two cases of six days, the two of seven days, and the one of eight days' duration the flow was considerable in amount as it extended over so many days but it occurred gradually. Proportionately to the amount of sediment there was a less number of epithelial cells than in the two specimens obtained from the patients whose periods lasted three days.

In as much as only practically normal cases had been selected the results show that there is some loss of epithelium during normal menstruation and that the amount of loss is dependent upon the severity and not necessarily upon the length of the menstrual period. There were certainly not enough epithelia in the discharge in any of the cases to suggest a complete loss of the superficial layer of the mucosa.

With the disappearance of the mentrual flow involution begins. We find that the blood vessels decrease rapidly in size as the engorgemnt lessens and that blood is no longer extravasated into the connective tissue spaces. What blood is left in the stroma is rapidly absorbed.

Granting now that there is a partial loss of the surface epithelium the question arises as to how this loss is repaired.

According to Leopold the surface epithelium which has been lifted from its bed, if the continuity has not been broken on all sides, resumes its former place and the lost epithelium is regenerated from adjacent cells. This is the consensus of opinion.

Sir John Williams, who claimed that the whole mucosa was destroyed, believed that the mucous membrane was regenerated from the epithelium of the glands which penetrated the muscle layer. Wyder, who taught the partial destruction of the mucosa, believed that there was a cell hyperplasia of the interglandular tissue in the deeper layer of the mucosa, which provides for the restoration of the loss of cells and that a regeneration of the superficial epithelium takes place from the gland epithelium and from the remaining " cell-islands."

Wendeler believed in a partial loss of the epithelium and that the necessary regeneration was accomplished as previously from a cell membrane situated under the base of the old epithelium containing flat, tender epithelium. No other investigator has observed such a membrane, however.

Mandl was the first, I believe, to demonstrate the various stages

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of well marked mitosis in the epithelium of the covering layer and showed that the lost cells were replaced by indirect cell division of the remaining cells. He believed that the gland cells also assisted in this process but did not agree with Von Kahlden who claimed that the formation of the new cells resulted entirely from those of the gland whose openings became widely extended and whose cells spread out in all directions.

The length of time necessary for the complete regeneration of the mucosa varies necessarily according to the amount of tissue lost. Williams believed that the entire mucous membrane was restored in a few days. Leopold states that the regeneration of the lost epithelium is performed likewise in a few days after the close of the menstrual flow. Westphalen, however, thinks that this process is a longer one consuming from six to eighteen days and believes that this stage is prolonged through the third or resting period as described by Leopold. In any event the interval between the complete restoration of the mucosa and the pre-menstrual congestion state is very short.

Whether the mucous layer of the Fallopian tubes undergoes a change during menstruation is a question. Personally I have not been able to examine the mucosa of the tubes removed during menstruation.

Mandl in one case, where he had removed the uterus and adnexia on the fourth day of menstruation, found that the mucous membrane of the tubes was swollen and hemorrhagic although the adnexia were normal.

Findley is the only observer who has exhibited a drawing of the mucous membrane of the tube during menstruation. He reports two cases in which the changes in the mucosa of the tubes were similar to those in the uterus, *i. e.*, there was a marked engorgement with blood, and free blood was found in the mucosa and in the lumen of the tube. The surface epithelium was found intact.

In conclusion we would offer the following resumé:

The menstrual cycle is divided into three periods; the first, preceding the menstrual flow and characterized by gradual development of a capillary congestion resulting in a serous or sero-sanguineous infiltration of the stroma of the mucosa, separating the cellular elements and gravitating toward the periphery forming collections of blood beneath the surface epithelium. Slight glandular hypertrophy as well as a swelling of the gland cells

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takes place, with a consequent hypertrophy of the whole mucosa. This stage is well exhibited in figure I, taken from a drawing by one of my students, Mr. Harry Rullison, to whom I would express my indebtedness, of a section of uterus removed immediately preceding the menstrual flow. A capillary engorgement and infiltration of the stroma, separating the cellular elements is especially noticeable in the outer portion. The enlarged cork-screw-like glands suggest a mild form of glandular hypertrophy.

The second stage of active hemorrhage is characterized by an outflow of blood through a diapedesis or through a rupture of the sub-epithelial hæmatoma, with more or less loss of the superficial epithelium depending largely upon the severity of the process. Figure II, a drawing of a section of a uterus removed the first day of the menstrual hemorrhage shows the infiltrated area near the surface with a breaking in the continuity of the surface epithelium allowing the blood an exit. In this plate the mucosa is drawn relatively too norrow.

In the third stage involution takes place. The engorgement of the blood vessels becomes quickly lessened and a rapid absorption of the blood in the stroma takes place. The epithelium which has been lost is regenerated by indirect cell division of the adjacent cells. This stage is prolonged until the premenstrual swelling begins or there is a slight interval during which the mucosa is inactive.

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Reprinted from ALBANY MEDICAL ANNALS, January, 1904.

THE ISLANDS OF LANGERHANS IN CONGENITAL SYPHILITIC PANCREATITIS.

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(*From the Bender Hygienic Laboratory, Albany, N. Y.*)

It is not my purpose in the present communication to give a detailed study of the lesions of congenital syphilitic pancreatitis. The condition is not important clinically, for it is found usually only in the still-born or in those dying shortly after birth; the pathology of the condition on the other hand, has been thoroughly studied and little can be added to the original description of Birch-Hirschfeld and the later systematic study of Schlesinger. The histological picture, however, shows a peculiar relation between the islands of Langerhans and the newly formed tissue which, as it has not been generally recognized and as it offers evidence in confirmation of our newer ideas concerning the anatomical and physiological independence of these structures, is I believe, worthy of special consideration. The study of the islands in this condition is also important, because occurring as it does in the foetus, it offers an opportunity to study the structures under adverse conditions of development, thus filling the gap between the normal development and the pathological changes seen in the adult organ.

Our recently acquired knowledge of the islands is almost entirely due to the work of Opie,[1] who has shown that a certain proportion of the cases of pancreatic diabetes have a definite relation to lesions of the islands of Langerhans. Upon these observations, which have been confirmed by several American and German investigators, is based the assumption that the islands

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have a physiology distinct from the remainder of the pancreas, and concerned especially with carbo-hydrate metabolism, therefore of prime importance in the pathology of diabetes. Very substantial support of this anatomical and physiological independence is offered by the experiments of Ssobolew[2] and Schulze.[3] These investigators, working independently, have shown that after ligation of the pancreatic duct in animals, the glandular portion of the organ atrophies and is replaced by fibrous tissue while the islands are unchanged and the urine remains free from sugar. Opie has observed a similar condition in the pancreas of man as the result of partial or complete duct obstruction by calculus or cancer.

It is this same picture of a chronic sclerotic inflammation with disappearance of the greater portion of the glandular structure and the persistence of the islands that is seen in the congenital luetic lesion of the pancreas. This persistence of the islands has not, however, been generally recognized, owing probably to the infrequency of the post-mortem examination of newly born children and in part to the fact that our interest in the pathology of the island has only recently been aroused. Previous to this awakening the only references are those of Schlesinger[4] and Condon[5] who merely mention the presence of the islands; while, since, Opie and Ssobolew the chief supporters of the theory of anatomical independence have offered this persistence of the islands as evidence in support of their view. At the time of their publications, however, our knowledge of the normal development of the islands was incomplete. This gap has been filled by my recent study[6] of the development of the island in the human embryo, and it is in connection with the results of this study that I wish to consider the changes in the syphilitic organ.

Literature of Congenital Syphilitic Pancreatitis. The first complete study of luetic pancreatitis of the new born was made by Birch-Hirschfeld[7] in 1875. In the series then reported, lesions of the pancreas were found in thirteen of twenty-three cases examined, but in a later series, in but twenty-nine of one hundred

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twenty-four. The frequency of the lesion in the second series agrees with the observations of subsequent writers.

The gross appearance of the organ is characteristic, the most striking feature being the increase in consistence, which in advanced cases approaches that of cartilage. An increase in size and weight is also quite constant. On section the surface of the organ is hard, white and glistening, the glandular appearance being entirely effaced. Birch-Hirschfeld compares the appearance on section to that of a fibroid; Cruveilhier, to that of a scirrhus cancer. Previous to Birch-Hirschfeld's study, this induration of the pancreas in congenital lues had been noted in isolated instances by Osterloh,[8] Cruveilhier,[9] Hecker,[10] Œdmansson[11] and Wegner.[12] The changes are most marked in the head of the pancreas, a fact which led Mraczek[13] and Beck[14] to consider the lesion to be an extension from the duodenum. Schlesinger states that there is no constant relation to syphilis of other organs, though the pancreas may be adherent to such.

Birch-Hirschfeld (1875) describes the lesion, histologically as an increase of connective tissue which compresses and causes atrophy of the glandular elements, without evidence of degeneration. Schlesinger (1898) gives a most complete histological study and decides that the increase of connective tissue is of perivascular origin. Contributions to the pathology of the lesion have been made also, by Huber,[15] Friedreich,[16] Mraczek, Müller,[17] Baumgarten,[18] Beck, Heubner,[19] Ssobolew, Opie and Condon. Gummata have been found only by Klebs,[20] Beck and Birch-Hirschfeld which is in striking contrast to the syphilitic lesion of the adult pancreas. Baumgarten and Cruveilhier describe a lardaceous appearance, but whether they use this term in the descriptive sense or to specifically refer to amyloid infiltration, is not clear from the text. Some difference of opinion exists concerning the period at which the lesion develops. Birch-Hirschfeld places it late in pregnancy; Schlesinger much earlier and quotes cases described by Müller and Mraczek in which it existed at the fifth month. Opie's statement that the almost complete absence of

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glandular tissue is due to arrested development rather than to degeneration indicates that he favors Schlesinger's view. It may be mentioned that the condition has been found five months (Birch-Hirschfeld) and three and a half years (Heubner) after birth. The involvement of the pancreas occurs in order of frequency after that of bone, lung, spleen and liver.

Material. My interest in congenital syphilitic pancreatitis was first aroused by Prof. Marchand of Leipzig, at whose suggestion I undertook an investigation of several minor points concerning the development and pathology of the islands of Langerhans. From the material of the Leipzig Institute, six specimens were obtained. Later while completing a study of the embryology of the islands, with the aid of material placed at my disposal by Prof. Mall of Baltimore, two additional examples were found. A single specimen was obtained from Dr. Flexner's collection of pancreas material and one also from the collection of Dr. George Blumer. I take this opportunity to thank these gentlemen for placing this unusual material at my disposal.

In all of these ten specimens the lesion is of the advanced sclerotic type with almost complete disappearance of the glandular elements. The early stages with infiltration of plasma and lymphoid cells are not seen. A careful study of the lesion adds practically nothing new to our knowledge of the general process. Selective stains prove the new tissue to be mainly of the white fibrous variety; the elastic tissue to be unchanged, or indeed in some instances, less in amount than in the normal pancreas. In one case very widespread mucoid degeneration of the new connective tissue was seen. Miliary gummata (syphilome miliare) were found in but one of the ten specimens.

The most striking feature is the persistence of the islands of Langerhans, despite the general destruction of the glandular acini. Throughout the dense fibrous tissue, with here and there the fragmentary remains of gland tissue, the islands stand out prominently, often surrounded by denser whorls of investing stroma, but apparently uninjured. (See illustration.) This

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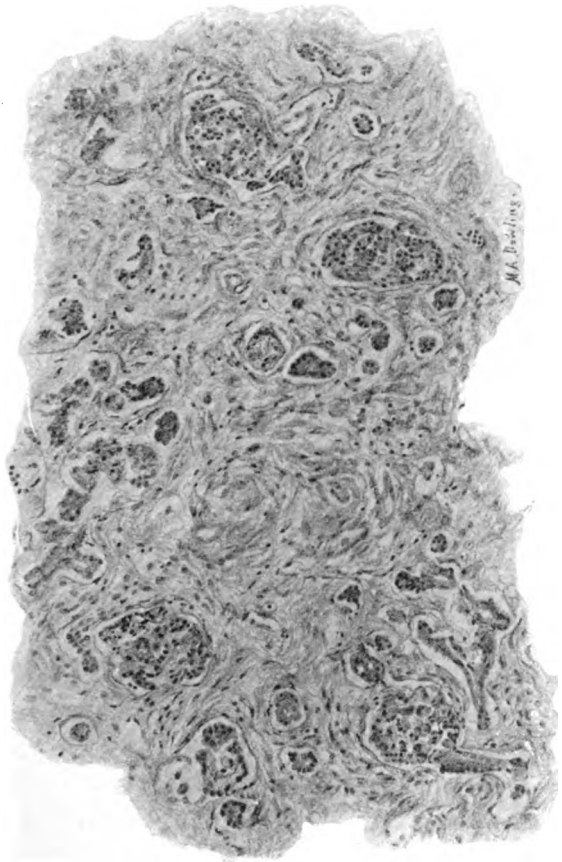
To Illustrate Dr Pearce's Article on "The Islands of Langerhans in Congenital Syphilitic Pancreatitis."

Albany Medical Annals, January, 1904.



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appearance is present constantly in all specimens and in all grades of the lesion, and the most careful search fails to reveal, in the islands, evidence of degeneration or atrophy, or the ingrowth of connective tissue. The absolute resistance of the islands to the process so destructive to the secreting portion of the gland is very strong evidence in favor of their anatomical independence and this condition, if considered in connection with our knowledge of the development of the islands, is very readily explained. While in most instances the islands appear entirely isolated, close examination shows that occasionally an island is connected with a glandular acinus by a stalk-like process of cells. This connecting band is in most instances a solid mass of epithelial cells; though, sometimes, a semblance of a lumen may be discerned. Opie alone, as far as I am aware, notes this band of cells connecting island and acinus. Upon this observation and the fact that no evidence of degeneration is seen in the island he bases the assumption that the island in its early development is in connection with the acinus and that its development is interrupted, in syphilitic pancreatitis, by the ingrowth of connective tissue which causes atrophy of the glandular tissue and leaves the more resistant island in its undeveloped state. At the time of Opie's communication our knowledge of the development of the islands was incomplete and especially so the manner in which the island became independent of the acinus from which it originated. That his assumption is correct, however, is shown by the results of my recent study of the development of these structures in the pancreas of the human embryo. These results may be briefly summarized as follows:

"The islands of Langerhans (embryo of fifty-four millimetres), originate through a proliferation and differentiation of the cells of the primitive secreting tubules. The differentiated cells characterized by a rich, finely granular, eosinophilic protoplasm lie as small round or oval masses in direct continuity with the cells of the tubule. Later, (embryo of about the third month) the attached portion becomes constricted, and lengthening, forms a a stalk-like, solid process of cells connecting the island with the

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acinus. At this period, a few entirely isolated islands are present. A separation takes place apparently brought about by the pressure of the investing connecting tissue. Vascularization has now occurred. In still later stages a progressive vascularization, increase of cells, arrangement of the cells in columns, and appearance of a fine reticulum is observed. The rapidly forming glandular structures finally surround the islands which then occupy the centres of the lobules."

From this summary it will be seen that in the pancreas of the third month the islands are still connected with the acini by solid processes of cells. The proportion of connective tissue at this time is very great, as the rapid glandular growth does not occur until the fifth and sixth months. Any disease of the pancreas occurring at this time would, therefore, influence the development of the organ, and evidence of this faulty development would be present at any subsequent stage of the lesion.

This seems to be the case in the lesion under consideration. Syphilis of the pancreas has been observed as early as the fifth month (Müller) and although there are no definite observations of its earlier occurrence, the appearance of the islands in the luetic pancreas when compared with the normal development of these structures indicates the possibility of the lesion occurring as early as the third month. The general microscopic picture of the normal pancreas at the end of the third month is very similar to the syphilitic organ at the sixth or seventh month, except that the latter has a larger proportion of connective tissue: *the same stage of development of the islands is seen in both.* In other words, at the latter period we have the development of the third month plus the connective tissue produced by the syphilitic lesion. It seems justifiable, therefore, to conclude that the syphilitic infection occurs at the period (third to fourth month) when the islands are still connected with the gland tubules, and that the newly formed tissue causes atrophy of the gland acini, but spares the more resistant islands. Thus is explained the similarity of the islands in the two conditions. The ultimate factor in this resistance of the islands is their abundant

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blood supply. That this vascularization of the island is not altered in syphilitic pancreatitis, I have demonstrated by the study of the diseased organ injected with Berlin Blue.

The evidence obtained by experiment and by the study of the pancreas of diabetics has already placed the theory of anatomical independence of the islands upon a substantial basis. The study of their development, has demonstrated that although they originate from the glandular tissue they eventually become wholly independent structures anatomically. It is with the object of adding still further confirmatory evidence, that this communication which adds nothing essentially new, but attempts to correlate known facts, is made.

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Reprinted from ALBANY MEDICAL ANNALS, October, 1904.

CANCER OF THE PANCREAS AND GLYCOSURIA.*

(A Histological Study of the Changes in the Islands of Langerhans)

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This investigation was undertaken for the purpose of determining what relation, if any, the islands of Langerhans may have to the glycosuria occasionally seen in connection with cancer of the pancreas. That pathological changes in these structures are frequently associated with diabetes has been satisfactorily demonstrated by the investigations of Opie[1] and others, and has led to a more definite knowledge of a form of diabetes which may properly be called pancreatic diabetes. No attempt has been made on the other hand, as far as I am aware, to demonstrate the presence of similar changes in connection with the glycosuria occasionally associated with cancer of the pancreas. That some of these changes—hyaline degeneration, chronic interacinar pancreatitis involving the islands and, according to a few investigators, diminution in the number of the islands—might result from the involvement of the organ by cancer is evident from our knowledge of the secondary lesions frequently accompanying such invasion. It is well known that duct obstruction, frequently the result of cancer of the head of the pancreas, readily causes a chronic pancreatitis; and it is possible also that the destruction of a large portion of the pancreas parenchyma by the new growth may destroy the islands to such an extent that they are no longer equal to the demands made upon them.

On the other hand we have no adequate explanation of those cases in which, though the pancreas is extensively or completely replaced by the new growth, diabetes does not exist.

*Previously published in the *American Journal of the Medical Sciences*, September, 1904, CXXVIII, 478.

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Such complete destruction, as in the cases reported by Litten[2] and v. Hansemann,[3] is analagous to the extirpation experiments by v. Mering and Minkowski,[4] but the absence of glycosuria is opposed to their results. v. Hansemann has attempted to explain the discrepancy by assuming that in primary cancer of the pancreas the tumor cells originating from pancreas parenchyma inherit the function of internal secretion peculiar to the normal cell. This explanation, however, is entirely hypothetical and in the light of our present knowledge of pancreatic diabetes loses its force unless we assume that all primary cancers of the pancreas arise from the islands of Langerhans, which, despite the recent publication of Fabozzi[5] supporting such origin, appears most improbable. If our newer theories concerning the relations of the islands to carbohydrate metabolism are firmly grounded, we should expect to find evidence of the persistence of the islands in such cases. With these various possibilities in mind, I have made a careful histological study of thirty cases of cancer of the pancreas, in three of which glycosuria was present.

The literature offers but scanty information concerning the frequency with which glycosuria occurs in connection with cancer of the pancreas. Such cases are not uncommonly reported but without reference to the occurrence of cases not complicated by glycosuria. From a hasty review of the subject, I believe the proportion (one in ten) shown by my cases to be high. We have, however, definite information concerning the reverse condition, that is, the frequency of cancer of the pancreas in connection with all forms of diabetes. In Oser's[6] series of 188 cases of diabetes, cancer occurred in 24; in Williamson's[7] series of 23, once; and in 139 cases reported by Windle,[8] in three. v. Hansemann's[9] tabulation of 72 cases of diabetes with pancreatic lesion contains five cases of cancer. I have examined many of the original descriptions of the cases quoted in these series with the object of determining if any peculiar macroscopic or microscopic conditions existed. The task has been most unsatisfactory for many of the reports are of a clinical nature and gross and histological description are meagre or entirely lacking. This analysis, however, confirms the well known clinical fact that in the majority of cases the new growth is in the head of the pancreas and by duct obstruc-

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tion causes an atrophy (chronic pancreatitis?) of the distal portion of the organ. This point is especially emphasized by v. Hansemann, Dieckhoff[10] and Windle.

The material upon which this study is based consists of the tissues from thirty cases of cancer selected from a group of thirty-five examples of new growth in the pancreas. As the material has been gathered from different sources, often from routine collections of autopsy material, it has not always been possible to procure tissues from the different portions of the uninvolved pancreas as well as from the cancerous portion, nor for the same reason, have essential data concerning clinical history and pathology been available in all cases.* Thus while all cases have been utilized in the study of the histological changes but twenty-one have been available, on account of incomplete examination of the urine, in arriving at conclusions concerning the occurrence of glycosuria. The thirty cancers studied may be classified as follows: primary in the head of the pancreas, nine; in other portions of the organ, 4; secondary to gall bladder or ducts, five; to stomach, eight; to breast, one, and to uterus, one. Glycosuria occurred in but three cases; in two of which the tumor was primary in the head of the pancreas; concerning the third, no clinical or pathological notes were available.

The results of the histological examinations, especially as concerns the islands of Langerhans are more readily described under the following headings: changes in (*a*) the immediate neighborhood of the new growth, (*b*) at a distance from the tumor, (*c*) in cases with extensive involvement, but no glycosuria, and (*d*) in cases accompanied by glycosuria.

(*a*) The important changes at the edge of the advancing cancer are the persistence and increase in size of the islands of Langerhans. While the glandular elements are invaded and replaced by the new growth and the newly formed connective tissue, the islands remain unaltered in the midst of the stroma, and occasionally, are even enclosed by a mass of tumor cells. Not only is this true of the edge of the tumor, but in the well infiltrated parts the islands may be seen in the stroma without

*I take this opportunity to acknowledge my indebtedness to Prof. F. Marchand of Leipzig Dr. Ludwig Hektoen of Chicago, Dr. F. B. Mallory of Boston, Dr. James Ewing of New York, Dr. W. G. MacCallum of Baltimore, Dr. W. T. Longcope of Philadelphia, Dr. M. Herzog of Chicago, and Dr. George Blumer, who have kindly placed material at my disposal.

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remnants of acini. The increase in size of some of these structures is four or five times that of the normal islands. These giant islands are typical in structure and readily distinguished from small alveoli of cancer cells. They represent a true hypertrophy of the islands and not altered pancreas acini.

(*b*) The changes at a distance from the tumor depend apparently upon the location and size of the same. With a cancer of the head of the pancreas causing pressure upon the duct a chronic interstitial pancreatitis of severe grade always existed, which, with the exception of one case to be described later, was always of the interlobular type. The islands persist in the midst of dense connective tissue and are not invaded by it. This condition has been observed by Opie in several similar cases without glycosuria.

A tumor at the head of the pancreas not obstructing the duct does not cause chronic interstitial changes. Small tumors of any portion of the pancreas are unaccompanied by changes in the islands of the normal portion of the organ; on the other hand, if the new growth is of considerable size, definite hypertrophy of these structures is apparent.

(*c*) But two cases of diffuse involvement of the organ occurred in this series; in neither was glycosuria present. These are, however, not analagous to those discussed by Hansemann, for areas of normal pancreas could be found here and there, lying in the midst of the new growth. In such areas were large islands, several times the normal size.

(*d*) Three cases of cancer of the pancreas accompanied by glycosuria are included in this series. One of these could not be utilized in the present study because of lack of data; the gross description of the pancreas not being available and the histological study incomplete inasmuch as only the tumor had been preserved and a study of the uninvolved portion of the pancreas was therefore impossible. The second case, a primary cancer of the pancreas involving the head only and accompanied by a slight intermittent glycosuria with free fat in the stools, showed no changes in the uninvolved portion of the organ. The islands were few in number and the increase in size usually seen in the immediate vicinity of the new growth was not evident. The third case was one of cancer of the pancreas with advanced chronic pancreatitis of the interacinar

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type. Sugar had been present in the urine for several months before death. The entire length of the pancreas was fifteen centimetres; the proximal five centimetres occupied by the tumor, the remainder of the organ atrophied and indurated. Histological examination revealed a severe grade of chronic pancreatitis with small scattered groups of more or less altered acini. Within these, smaller strands of connective tissue had penetrated, involving to a varying extent, the islands of Langerhans.

While it is impossible to draw any definite conclusions from such a small number of cases, these observations are very suggestive and offer some support of the newer ideas concerning the anatomy and physiology of the islands. The persistence of the islands in the midst of the tumor stroma supports the theory of anatomical independence, an independence which I have recently definitely demonstrated by a study of their development.[11] This persistence is analagous to that described by Schlesinger,[12] Opie, Condon[13] and Pearce[14] in congenital syphilitic pancreatitis, and by Opie in various other sclerotic conditions of the organ. The increase in size of the islands suggests a purposeful enlargement due to increased function and therefore of the nature of a compensatory hypertrophy. A similar hypertrophy of these structures has been described by Warthin[15] and by Ohlmacher[16] in connection with cancer of the liver, and is considered by them, also, to be compensatory in nature, compensating, however, for the lost or limited liver function. The livers of my cases have not been available in all instances for histological examination, and I have not therefore been able to arrive at any conclusion concerning the relation of enlarged islands to lesions of that organ. It is possible that a relation of a compensatory nature may exist between the carbohydrate metabolism of the liver and the islands of Langerhans; but the hypertrophy of the latter structures when associated with cancer of the pancreas is, I believe, an attempt to compensate for the function of the lost islands.

The cases of diffuse cancer of the pancreas without glycosuria can be explained only on the supposition that the amount of normal pancreas remaining is sufficient to furnish the secretion necessary to carbohydrate metabolism. v. Mering and Minkowski found in their extirpation experiments that if one-

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fourth to one-fifth of the pancreas remained, diabetes did not result; a destruction of the pancreas by cancer we may consider analagous to partial extirpation. In both of my cases of diffuse cancer, small areas of pancreas containing islands could be found in the midst of the new growth in a sufficient amount to correspond to the unextirpated fifth. In this connection the possibility of an accessory pancreas (Thorel,[17] Sweet[18]) or other glands maintaining the balance of function must also be considered. v. Hansemann's explanation of the absence of glycosuria is not applicable unless we assume that all cancers of the pancreas arise from the cells of the islands of Langerhans.

Finally we have the cases with glycosuria. In one of these a true diabetes existed, in the other an intermittent glycosuria. The first is readily explained by the presence of an interacinar pancreatitis with involvement of the islands, a type of pancreatitis originally described by Opie in connection with diabetes and since observed by many investigators. It therefore appears that while cancer of the head of the organ with duct obstruction may frequently cause a chronic pancreatitis, glycosuria does not result unless the interacinar form with involvement of the islands develops. This naturally brings cancer diabetes into a common relation with pancreatic diabetes in general.

The case of intermittent glycosuria brings up the vexed question of alimentary glycosuria. It is well known that a normal individual may digest without disturbance from 150 to 250 grammes of sugar, but that an increase over this amount may lead to temporary excretion of glucose in the urine. This excretion, due to hyperglycemia, is the inevitable result of a sudden flooding of the circulation with an amount of glucose beyond that which the body is able at once to consume. On the other hand, in a number of abnormal conditions where there is no actual diabetes, an alimentary glycosuria may be produced by an amount of sugar which in the economy of the normal individual is easily consumed. Among the prominent conditions in which this occurs may be mentioned neuroses, traumatic or otherwise, organic nervous diseases, alcoholism, infectious diseases, exophthalmic goitre, hepatic and pancreatic disease. Is it not possible that this temporary excretion of sugar is due to some transient disturbance of the function

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of the islands brought about by vascular disturbances of the islands or by some toxic substance, perhaps of the nature of an autotoxin, affecting the secretion of these structures or temporarily throwing them out of function? In a destructive disease of the pancreas, as cancer, a certain number of the islands are necessarily destroyed; the remainder, however, may be sufficient under normal circumstances to furnish the necessary secretion, whatever it may be, essential to carbohydrate metabolism; but if overtaxed by an unusual injection of glucose, hyperglycemia and a consequent glycosuria might result. This explanation has occurred to me in connection with my case of cancer accompanied by intermittent glycosuria; and that it is not entirely hypothetical is indicated by the observations of Ssobolew,[19] confirmed by Herzog,[20] that in some cases of permanent diabetes the pancreas exhibits a great diminution in the number of islands, and in some cases, an entire disappearance. This deficiency, however, is far from proven, and in mentioning it I do not wish to be placed in the position of advocating a pancreatic origin for all forms of diabetes.

Conclusions—We have a definite basis for ascribing a certain portion of the cases of diabetes to lesions of the pancreas and ultimately to lesions of the island of Langerhans. As a result of the study here briefly outlined we can, I believe, include the permanent diabetes of cancer of the pancreas in this group. Further observations must be made before the intermittent glycosuria can be attributed to destruction of large numbers of islands. The absence of diabetes in cases of extensive involvement of the pancreas would appear to be due to the survival of small fragments of the pancreas including a sufficient number of islands to carry on their peculiar function. The persistence of the islands under the adverse conditions described supports the observation heretofore made concerning their anatomical independence, while their enlargement, suggesting as it does a compensatory hypertrophy, is corroborative of the theory that they have an independent special function.

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Reprinted from the ALBANY MEDICAL ANNALS, May, 1904.

EXPERIMENTAL PANCREATITIS CONSIDERED IN ITS RELATION TO THE ACUTE FORMS OF PANCREATITIS IN MAN.

Presented before the Medical Society of the Greater City of New York, February 8, 1904, in a discussion of "Diseases of the Pancreas."

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The short space of time allotted me in this discussion will not allow a comprehensive statement of the many fruitful experimental researches having for their object the elucidation of the physiology and pathology of the pancreas. Various phases of the experimental investigations will, doubtless, be taken up by others who address you this evening; and I have therefore, with the approval of your president, decided to limit my remarks to a consideration of the acute lesions which may be produced experimentally. What we have gained by experiment in this field is practically a knowledge of etiology, and it is therefore more particularly the question of etiology that I will discuss. I will not hesitate moreover to compare the experimental lesions with the acute lesions seen in man, with the object as far as possible of correlating the knowledge gained by experiment and that gained by pathological study.

In any consideration* of the acute forms of pancreatitis we are confronted at the outset with the question of classification. The division into hæmorrhagic, suppurative and gangrenous forms as made by Fitz would appear to satisfy all demands. Some writers, however, speak of a necrotic form. This is of doubtful value, for all forms show more or less necrosis; indeed, in the hæmorrhagic form, especially that produced experimentally, necrosis is a constant and essential part of the process, though not always evident macroscopically. The possibility of pancreatic hæmorrhage without inflammation—the so-called pancreatic apoplexy—

* In the preparation of this brief summary I have freely used the recently published work of Opie (Diseases of the Pancreas, Its Cause and Nature, J. B. Lippincott Co., 1903) and Flexner's description of the pathological anatomy of the pancreas (Transactions of the Congress of American Physicians and Surgeons, 1903, vi, 18); and I take this opportunity to acknowledge my indebtedness. I have not attached a bibliography. All references may be found in the bibliography of Opie's work.

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is another debatable question which, in the present state of our knowledge cannot be definitely settled. It seems probable from our present point of view, that thorough histological examinations of such cases would furnish evidence of inflammatory changes and bring this lesion under the head of hæmorrhagic pancreatitis. Seitz, the last writer (1892) to make a careful study of this lesion is, however, opposed to this view and believes that some cases, at least, may be attributed to arterio-sclerosis.

Hæmorrhagic Pancreatitis.—The gross appearance of this form of pancreatitis—an enlarged organ with diffuse or mottled hæmorrhagic areas of varying color and greyish-white spots or streaks of fat necrosis—is so well known that we may turn at once to the question of etiology. Our knowledge of the causes of pancreatitis is entirely the result of experiments having for their object the reproduction of the condition. Clinical observations have contributed nothing, and with the exception of Opie's observations upon the relation of cholelithiasis, the same may be said of general pathological examinations. The simplest form of experimentation is the injection into the pancreatic duct of various irritating or supposedly injurious substances. A great variety of substances thus introduced have been found to produce typical hæmorrhagic pancreatitis, usually with fat necrosis. These substances are deliquescent zinc chloride (Thiroloix), artificial gastric juice (Hlava, Flexner and Pearce) bile (Opie, Flexner and Pearce), papaine (Carnot), and bacteria and their toxins (Hlava, Carnot, Flexner). Various other substances as formalin, nitric and chromic acids, and solution of caustic alkalies, Flexner found would produce the same results. The disease produced by these various agents usually runs a rapidly fatal course, though some animals may live for weeks and present at death extensive suppurative or sclerotic changes. In some instances putrefactive micro-organisms invade the injured organ and cause a gangrenous pancreatitis. If we study these various methods with the view of determining if any of them may operate to cause the hæmorrhagic pancreatitis seen in man, we have four possibilities: action of (*a*) ferments originating in the pancreas, (*b*) bacteria, (*c*) gastric juice, and (*d*) bile.

The possibility of the first is suggested by Carnot's experiments with papaine, and some support is offered by Chiari's

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observations upon autodigestion of the pancreas. According to Chiari this change occurs shortly before death and may be accompanied by multiple small hæmorrhages. The destruction of the parenchyma thus brought about affords an opportunity for the diffusion of the pancreatic ferments. There is some evidence that fat necrosis may be caused by the fat splitting ferment thus liberated, but as yet we have no definite proof that a true hæmorrhagic pancreatitis may result from the action of this or other ferments liberated at the same time.

Various micro-organisms, as the bacillus coli, the pneumococcus and the pyogenic cocci have been found, not infrequently, associated with hæmorrhagic pancreatitis. There has been no uniformity in these findings and most of the writers reporting the results of bacteriological examinations agree that the organisms represent a secondary invasion of injured tissue and are in no way concerned in the etiology of the lesion.

That the gastric juice, as suggested by Hlava may enter the pancreatic duct and produce an inflammation of the pancreas presupposes a powerful anti-peristaltic, or other action, forcing the secretion into the duct. Of such action we have no definite evidence. Under normal conditions it is practically impossible to force fluids from the intestine into either bile or pancreatic ducts. I have recently made some experiments upon dogs in order to determine this point. The intestine was ligated at varying distances above and below the orifice of the ducts and distended by injecting colored solutions and suspensions. After varying periods of time, the animals were killed, but no staining of the ducts could be demonstrated. In other experiments upon the dead animal, forcible manual pressure was exerted upon the similarly ligated intestine with negative results. On the other hand it cannot be denied that under certain pathological conditions of the duct orifice, intestinal fluids may possibly be forced into the duct. Concerning the negative action of the natural gastric juice upon pancreas parenchyma the following case would appear conclusive:

(*Records of the Pathological Department of the University of Pennsylvania; Autopsy No. 0.148.*) The clinical history of this case is brief and incomplete. The patient, a negro, aged forty-one, was admitted

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to the Insane Department of the Philadelphia Hospital on July 19, 1900, with a diagnosis of delusional insanity. For the next six months his condition, apparently, was not noteworthy. "On January 28, 1901, patient seemed to be rather dull and was put to bed." On February 11th, regurgitation of blood mixed with milk curds was observed. This continued until his death, on February 13th. Physical examinations revealed a rather firm mass in right hypochondriac region, which, upon palpation caused patient to complain of pain. At no other time did he complain of pain. Temperature normal, pulse about 100 and of poor volume; no distention of abdomen; marked constipation. Albumen was found in the urine; and microscopically, numerous hyalin and granular casts. The clinical diagnosis was cancer of the stomach and the liver with chronic nephritis.

Autopsy—Pathological diagnosis: Recent hæmorrhage in and about pancreas and duodenum, chronic gastro-pancreatic fistula; chronic interstitial pancreatitis; chronic pulmonary tuberculosis; tubercolosis of bronchial, gastro-hepatic and retro-peritoneal lymph nodes; chronic mitral endocarditis; general chronic passive congestion; chronic diffuse nephritis (parenchymatous type).

Abdominal cavity: Stomach greatly dilated, the lower margin extending below the umbilicus; pylorus touching right costal margin. Beneath the pylorus and entirely surrounding the duodenum is a globular, firm, hæmorrhagic mass, distinctly encapsulated and resting on the upper end of the right kidney. The subperitoneal tissues between the stomach and the transverse colon and in the neighborhood of pylorus and adjacent abdominal wall are infiltrated with clotted blood. Stomach, pancreas, duodenum and transverse colon with hæmorrhagic mass removed entire. Upon opening the stomach it is found to be normal except for the presence of a small orifice with smooth edges four centimeters from the œsophageal end. The outer wall of the stomach about orifice is bound to the pancreas nine centimeters from its splenic end by dense fibrous adhesions. A probe passed through the orifice in the stomach enters a sinus leading to the pancreas. This sinus passes directly through the pancreatic tissue. Its walls are lined by dense fibrous tissue, and it contains blood-stained mucus-like fluid. The canal can be followed for a distance of five centimeters. It then approaches the surface of the pancreas where it is continuous with the blood clot about the duodenum. No foreign body is found in the sinus. The splenic end of the pancreas for a distance of eight centimeters appears normal; the middle portion for a distance of four and a half centimeters is paler and firmer than normal, and the lobulations are not so distinct; through the remaining five centimeters constituting the duodenal end, the pancreas is extensively infiltrated with blood. Surrounding the duodenal end of the pancreas and completely encircling the duodenum is an encapsulated mass of black clotted blood fourteen centimeters in length and seven centimeters in diameter. The long diameter of this clot corresponds to the course of the duodenum. The source of the hæmorrhage cannot be discovered. The pancreatic and common bile ducts are patulous. The mucous membrane of the duo-

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denum is very thin, blood-stained, and at one point presents a small adherent blood clot two centimeters in diameter. No fat necrosis.

Histological examination: The wall of sinus is composed of dense fibrous tissue. On its surface is a thin layer of granular material with a few pus cells. Sections stained by the Gram-Weigert method show a few cocci and bacilli. Scattered through superficial portion of sinus wall are many lymphoid and plasma cells and a few polymorphonuclear leucocytes. New blood vessels are seen throughout, and here and there are small areas of hæmorrhage. In the deeper portions the hæmorrhage is more diffuse, and here are seen small islands of atrophic pancreatic tissue infiltrated by lymphoid cells. From the sinus wall coarse bands of fibrous tissue run into the substance of the pancreas, and divide into finer lines which penetrate the pancreatic acini. Sections from various portions of the pancreas, at a distance from the sinus, show a moderate increase of perilobular connective tissue. The cells of the parenchyma are very granular and stain poorly. The islands of Langerhans are prominent and unaltered. Throughout the duodenal portion extensive hæmorrhage is seen in the interstitial tissue, penetrating in places the parenchyma which is œdematous. No necrosis or exudation is evident. The splenic portion is free from hæmorrhage.

From this description it is evident that in the early development of the sinus the gastric juice must have been in intimate contact with the pancreas parenchyma but failed to produce a hæmorrhagic pancreatitis. The hæmorrhage into the duodenal portion, was unaccompanied by acute changes and was due apparently to extension from the large clot about duodenum. The chronic pancreatitis was merely a localized process about the sinus. The case offers strong evidence against the possibility of gastric juice exciting a typical hæmorrhagic pancreatitis.

The relation of bile to acute pancreatitis has received very substantial support from experimental observations and also from the not unusual occurrence of the lesion with cholelithiasis. The most important contributions to this phase of the subject have been made by Opie, who has worked out the pathogenesis of pancreatitis associated with gall-stones and by injecting bile into the pancreatic duct of the dog has produced a typical inflammation of the gland with associated fat necrosis. In one particularly fortunate autopsy he found at the apex of the diverticulum of Vater a small calculus completely blocking the duodenal orifice but too small to obstruct the orifices of the common bile and the pancreatic duct. These ducts were thus transformed into a continuous closed channel from which it was impossible for

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their respective contents to escape. Upon dissecting the pancreatic duct it was found to be stained light green with bile, indicating that the slightly greater pressure in the bile duct, probably due to the contraction of the gall-bladder, had forced bile into it. An acute hæmorrhagic pancreatitis with disseminated abdominal fat necrosis existed.

The same writer has also analyzed the reported cases of acute pancreatitis and finds that cholelithiasis is very constantly associated with the hæmorrhagic and gangrenous forms of the lesion. On the other hand, acute pancreatitis is a rare condition as compared with the relative frequency of cholelithiasis. In this connection it is important to point out, as Opie has done, that in only a small proportion of individuals (in about three out of ten) are the anatomical features such as to allow favorable conditions for bile to penetrate the pancreatic duct. The ducts, in a considerable number of individuals (ten per cent.) open separately and the diverticulum does not exist. Also, the size of the diverticulum bears an important relation to the production of the condition; its variation in length is from zero to eleven millimeters; the average diameter of the orifice being two and a half millimeters. In only thirty of Opie's 100 examinations did the length reach five millimeters. Thus it is evident that a stone to produce obstruction of the duodenal orifice only, must be relatively smaller than the diverticulum, for otherwise the orifices of both ducts would also be obstructed and the secretions forced back upon their respective organs.

While cholelithiasis is thus definitely established to be an important factor in the etiology of acute pancreatitis, it does not explain all cases. Many cases have been reported in which neither clinical history nor autopsy affords evidence of cholelithiasis, though it is noteworthy that since attention has been called to this association these cases are not so numerous. It should also be noted in this connection that the stone after obstructing the papilla orifice and causing a pancreatitis may pass into the intestine and escape observation, or perhaps pass from the intestine entirely A dilatation of the diverticulum may in such cases indicate the previous resting place of the stone. The following case would appear to be an example of this kind:

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Clinical abstract: Patient of Dr. W. E. Fay, of Boston, Mass.—Robust woman, aged thirty-six, with history of occasional sharp attacks of gastro-enteritis after excessive indulgence in wine. "The mortal attack began with a 'French' dinner on Thanksgiving Day. From claret she changed to whiskey, drinking considerable between November 29th and December 8th. When first seen on the latter of these dates she was tremulous and sleepless, with wild look in the eyes, intense burning in epigastrium and violent and continuous emesis. Neither water nor cracked ice could be retained. The vomitus was green, thin and acid. After hypodermic use of morphine and careful administration of chloroform, almost steadily for an hour, sleep was obtained lasting three hours. Restlessness then returned, with frequent hiccough, and ceaseless cry for water, which was rejected in whatever quantity or temperature given. Washing of stomach, and paraldehyde administered by enema afforded temporary relief. Abdomen was distended. Obstinate constipation was overcome by high enemata. Persistent flatulence was present in both stomach and bowel, and considerable pain centering in the epigastrium and extending throughout the abdomen. This condition continued with temporary alleviations for nine days after she was first seen. Then, December 17th, slight jaundice was noticed. The patient desired nothing but frequent drinks of milk and limewater. December 20th the patient sitting up and begins to eat gruel, but has no energy. December 24th, sudden enlargement of right parotid and adjoining glands with redness extending below angle of jaw; considerable emaciation has taken place. After sitting up parts of two or three days, which was agreeable to her, there was increase of tenderness throughout the abdomen. Temperature rose to 101 degrees. Distention was constant, free fat appeared in the urine; sugar was present. The patient sank rapidly and died on the 30th."

Autopsy, performed six and one-half hours after death.

Anatomical diagnosis: Hæmorrhagic and gangrenous pancreatitis with fibrinous peritonitis and accumulation of grumous fluid in peritoneal cavity. Multiple fat necroses of omentum, mesentery, epiploic appendages and subperitoneal fat generally. Acute duodenitis with dilation of orifice of duodenal papilla. Localized dilatation of common bile duct. Dilatation of pancreatic duct. Fatty degeneration of heart, liver and kidneys. *Abdomen*—Excessive amount of subcutaneous fat. Omentum, mesentery, epiploic appendages and abdominal fat generally closely studded with round or oval greyish-white areas two to five millimeters in diameter and distinctly circumscribed. Many of the greatly enlarged epiploic appendages (3 x 1.5 cm.) are entirely necrotic. In pelvis and both flanks is a thin greyish-red greasy fluid containing small black shreds of friable material. Omentum is glued to anterior abdominal wall by a blood-stained fibrinous exudate. A similar exudate covers the coils of the small intestine. The position of the pancreas is occupied by a soft friable, irregular reddish-black mass 4 x 1.5 centimeters, freely moveable. The cavity in which this mass lies is lined by reddish-black necrotic tissue, which adhere in places to colon and stomach. The mass on section shows at splenic end irregular areas of greyish pancreatic tissue separated by dark red

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lines of hæmorrhage and necrosis. Elsewhere it is uniformly necrotic. *Duodenum*—Contains material similar to that about pancreas and its mucosa is injected. The orifice of papilla is dilated and in the duct one centimeter from the orifice occurs a circular dilatation with smooth walls, one and five-tenths centimeters in circumference. No calculi are found in gall-bladder, ducts or intestine. The pancreatic duct is dilated and separated from the pancreas; a probe from duodenal end passing directly into the cavity about the gangrenous pancreas. Bacillus coli was found in the necrotic material about the pancreas.

While this case is not conclusive, in as much as the stone was not found, the anatomical condition indicates that a calculus, at some time, was lodged in the common duct and the possibility of later occlusion of the papilla with final discharge of the stone is evident.

The Sequence of Histological Changes in Hæmorrhagic Pancreatitis.—Much discussion has arisen concerning the precedence and succession of the three principal phenomena—hæmorrhage, necrosis and exudation. Katz and Winkler believe that the necrosis follows hæmorrhage and is the direct result of injury produced by the extravasated blood. Hlava found extensive occlusion of the blood vessels after acid injection and considered it to be the cause of both necrosis and hæmorrhage. Opie found hæmorrhage intimately associated with necrosis and followed only secondarily by inflammatory changes. From his earlier experiments Flexner drew the conclusion that hæmorrhage and necrosis are the result of the simultaneous action of the injurious agent upon blood vessels and tissue, and that they occur coincidentally. In a later series of experiments by Dr. Flexner and myself an attempt was made to definitely settle these mooted points. Dogs under choretone narcosis received injections of one to two per cent. solutions of hydrochloric acid into the duct and directly into the parenchyma of the pancreas. Small portions of the organ were removed after periods varying from thirty-five minutes to eight hours and examined histologically. It was found that hæmorrhage, hyalin necrosis and exudation of fluid and leucocytes could be readily demonstrated in tissue removed one hour after injection. Sections taken at the end of eight hours represented the pathological process at its height. That these lesions are correlated in the pancreas may therefore be considered as demonstrated.

At the same time in order to determine the effect of red

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blood corpuscles upon the pancreatic tissue, a condition analagous to hæmorrhage was brought about by the injection of sterile defibrinated dog's blood through the duct and directly into the parenchyma. Such injections did not set up an acute pancreatitis but were followed by chronic proliferative changes. Similar injections of dog's serum were negative.

Gangrenous Pancreatitis.—Experimental and post-mortem observations both indicate that in the majority of cases gangrenous pancreatitis is secondary to an acute hæmorrhagic inflammation of the organ. The tissue, primarily the seat of hæmorrhage, necrosis and inflammation readily becomes gangrenous under the influence of putrefactive micro-organisms invading it from the intestinal canal. The association of hemorrhage and gangrene frequently seen at autopsy was first emphasized by Fitz, who also recognized however the possibility of the lesion originating from perforating inflammation of the gastro-intestinal canal or of the biliary passages.

In the series of experiments by Dr. Flexner and myself, two examples of gangrenous pancreatitis following acid and bile injections respectively, occurred. Death occurred in each instance in less than twenty-four hours, and the gangrenous portions of the pancreas were studded with emphysematous blebs. Films showed bacilli having the morphology of B. aerogenes capsulatus. Futhermore, gangrenous pancreatitis has the same relation to cholelithiasis as has the hæmorrhagic form. In Opie's table of thirty-seven cases of acute pancreatitis associated with cholelithiasis, eight are described as hæmorrhagic and gangrenous and thirteen as gangrenous. Disseminated fat necrosis is a striking feature of this lesion.

Suppurative Pancreatitis.—Suppurative inflammation of the pancreas, unlike the hæmorrhagic and gangrenous forms, does not differ essentially from that of other organs. It may be primary or secondary. The relation of the pancreas to the intestine allows the possibility of infection through the duct, while lesions of adjacent hollow viscera may extend directly or as the result of perforation. In general infection of the blood, pyæmic abscesses may develop in the pancreas as in other organs. Direct extension of an infectious pylephlebitis may also occur. These lesions are seldom accompanied by extensive necrosis, hæmorrhage or dissemi-

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nated fat necrosis. The accumulation of pus is not diffuse but occurs usually as localized abscesses. Hæmorrhage and necrosis if present are generally focal in character, suggesting the local action of an irritant. Rarely the pancreas may be entirely destroyed and appear as a sequestrum in a pus cavity. Experiments, especially those of Flexner, show that abscesses of the pancreas may follow the injection of various fluids, as weak solutions of hydrochloric, sulphuric and nitric acids, sodium hydrate and suspensions of the B. pyocyaneus. In these experiments we have evidently a primary necrosis due to the irritant and a secondary invasion by micro-organisms. Körte, in a few instances, produced abscesses by injecting pus containing a bacillus of the colon group. These experimental lesions are seldom accompanied by fat necrosis. A study of the lesion in man and of the experimental findings indicates that this suppurative form of pancreatitis is due to some local influence causing limited necrosis and suppuration. There is, however, some evidence that duct obstruction may rarely lead to the condition probably in that it favors the entrance of bacteria. In Opie's table, previously quoted, "purulent pancreatitis" occurred in four of forty-one cases complicated by cholelithaisis. The common duct in only one of these, however, contained a stone. The following case illustrates suppuration of the pancreas with fat necrosis, accompanying cancer of the diverticulum and cholelithiasis:

Records of the Bender Laboratory, Autopsy No. 0.676. Clinical abstract: The individual, a male aged seventy-three, patient of Dr. A. W. Elting, was admitted to the Albany Hospital on August 24, 1903, with a history of hepatic colic which began on August 15th. Since May 1st he had suffered from gastric distress, nausea and dull pain in region of stomach, and had lost in strength and weight. Physical examination reveals a jaundiced, emaciated, feeble individual with evidence of arterio-sclerosis, enlarged heart and emphysema of the lungs. Upon palpation of abdomen a distinct irregular tumor mass was felt in the epigastrium; deep pressure elicited some tenderness. During patient's sojourn in the hospital there was slight change in his condition. The jaundice continued and nausea after the taking of food persisted. The pain subsided. Physical examination revealed nothing new. Emaciation and weakness progressed rapidly, and death occurred on September 11th.

Autopsy, by Dr. A. T. Laird, twelve hours after death.

Anatomical diagnosis: Cancer of the diverticulum of Vater with ulceration of duodenum and metastases in liver; dilatation of common duct and gall-bladder; cholangitis, gallstones free in colon; jaundice;

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multiple abscesses of head of pancreas; peripancreatic fat necrosis; hæmorrhage into intestine; arterio-sclerosis.

The individual is extremely emaciated and jaundiced. In *duodenum*, about one and a half centimeters above duodenal papilla, is a circular ulcer three centimeters in diameter with irregular edges and firm indurated bile-stained base. The base of the ulcer, five millimeters in thickness, rests upon the head of the pancreas to which it is intimately adherent and upon indurated lymph nodes. The tissues beneath the papilla are infiltrated by a dense greyish-white diffuse growth of new tissue. The duodenal papilla is prominent and rests on the indurated mass below it; bile readily flows from its orifice on forcible pressure of gall-bladder. Common duct is slightly dilated. Gall-bladder measures ten centimeters in length and is distended with thick fluid bile, no calculi present. *Liver* is of a dark uniform greenish color, and bile ducts are distended with thick bile. Scattered throughout the organ are numerous greyish-white firm areas, one-half to two centimeters in diameter, of fairly definite outline. *Pancreas* measures fourteen centimeters in length. The duodenal end for a distance of five centimeters is irregularly swollen. On section a yellowish purulent fluid escapes and the cut surface presents numerous abscesses of varying size with thin trabeculated walls. The middle portion of the organ is firmer than normal. Splenic end is unaltered. Duct patent though its proximal portion is surrounded by the new growth. Peripancreatic fat presents numerous distinctly circumscribed yellowish opaque areas. The small intestine is blood-stained throughout its length and contains an accumulation of blood, fluid and clotted. A lesser amount of blood is found in the large intestine. The source of the hæmorrhage is apparently the ulcer in the duodenum. In the lower portion of the discending colon are found two smooth facetted calculi composed of cholesterin and inspissated bile. *Histological examination* shows a cancer about and involving the diverticulum and the common duct with extension to the duodenum and to the head of the pancreas and with metastases in the liver. The head of the pancreas is the seat of advanced perilobular pancreatitis, in the midst of which are numerous abscesses. These abscesses are chronic in character, and contain much necrotic material and zoogloea of large thick bacilli. The tail of the pancreas is the seat of a slight perilobular pancreatitis. Typical fat necroses are numerous. The ducts are dilated and contain an accumulation of mucous and desquamated epithelial cells.

Fat Necrosis.—This condition is so constantly a comcomitant of acute pancreatitis and its elucidation so entirely the result of experimentation that a consideration of the experimental lesions of the pancreas would be incomplete without reference to it. Hæmorrhagic and gangrenous pancreatitis, as they occur in man or as the result of experiment, are generally accompanied by this peculiar lesion of the fat tissue. Rarely it occurs in connection with suppura-

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tive lesions, and occasionally, as will be pointed out later, with chronic interstitial pancreatitis. The characteristic appearance is that of small round or oval areas white or greyish-white in color and usually sharply circumscribed. Microscopic examination shows these areas to be composed of necrotic fat cells. In early necroses fatty acid crystals may be demonstrated. These areas are found most abundantly in the neighborhood of the pancreas and are usually limited to the abdominal fat, but they may be widely disseminated and appear in the fat beneath the pericardium and the pleura, in the subcutaneous fat and in the marrow of long bones. Fitz first suggested that fat necrosis is the result of a lesion of the pancreas, but to Langerhans belongs the credit of first demonstrating the essential nature of the process. By chemical and histological studies he showed that the changes within the fat cells are associated with the splitting of the fat molecule into its fatty acid and glycerine. The glycerine is absorbed and the acids are deposited in the cells as needle-like crystals. The cell loses its nucleus and is apparently necrotic. Later, chronic proliferative changes occur about the areas. Leucocytes may enter the necrotic fat but when numerous, indicate invasion by bacteria. Although bacteria have been frequently found in these necroses they are not concerned in the production of the lesion and must be considered as secondary invaders. Instances in which the injection of bacteria into the pancreatic duct has resulted in the necrosis of fat are to be explained by the setting free of pancreatic ferments as the result of injury to or inflammation of the gland.

The first experimental proof of the relation of fat necrosis to pancreatic ferments was offered by Langerhans, who injected suspensions of the comminuted pancreas of the rabbit and dog into the perineal fat of the rabbit. One of his thirteen experiments was successful and he concluded that these necroses are due to the action of the fat splitting ferment of the pancreatic juice. Jung obtained similar results by introducing portions of the fresh pancreas of one animal into the adbominal cavity of another; Hildebrand and Dettmer, Williams, Whitney, Flexner, Milisch, Körte and Opie have obtained similar results by various injuries allowing the escape of the pancreatic juice into the adjacent fat and the peritoneum. Their methods include ligation of

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ducts and vessels; ligation, laceration and incision of the parenchyma; and excision of portions of the organ. The experiments of Hlava, Körte, Oser, Opie, Flexner and Pearce, in which an acute pancreatitis, usually hæmorrhagic, has followed the injection of various substances as acids, alkalies, gastric juice, bile, bacteria, etc., have also caused the appearance of fat necrosis. In these experiments the fat necroses are not due to the substance injected but to lesions of the pancreas which allow an escape of the pancreatic juice. The final link in this chain of experimental evidence was Flexner's demonstration, by chemical test, of the presence of a fat splitting ferment in the necrotic foci. Portions of the necrosed foci, from both human and experimental cases, when brought in contact with neutral butter fat caused a splitting of the fat with the freeing of fatty acids recognizable by their odor and reaction.

It has been claimed by some writers, especially by Oser, that the presence of a fat splitting ferment will not explain the widely disseminated necroses, such as occur in the subpericardial, sub-pleural, and sub-cutaneous fat. Opie has, however, in a series of duct ligations demonstrated by Flexner's method the presence of the fat splitting ferment in the distant necroses of the subcutaneous and subpericardial fat as well as in the peri-pancreatic foci. The diffusion of the ferment in these experiments he also found was hastened when the secretory activity of the pancreas was stimulated by injection of pilocarpine.

Wells (*Journal of Medical Research*, *1903*, *ix.*, *70*) has found that commercial "pancreatin" will produce typical fat necrosis, but that this power is lost after heating for five minutes at some point between sixty-five and seventy-one degrees centigrade. Its power to produce fat necrosis decreases proportionally as the temperature is raised above fifty-five degrees Centigrade. These observations indicate an enzyme action as the source of the lesion. He was unable, however, to determine which of the pancreatic enzymes causes fat necrosis, and could not produce fat necroses with the lipolytic extracts of hog's liver or cat's serum used either alone or in combination with trypsin. He thinks it possible that the lipase causes fat splitting after some other ingredient of the pancreatic juice has injured the cell; fat splitting is subsequent to the necrosis and not its cause. The lipase normally

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in fat tissues exerts no fat splitting effect upon necrotic fat if the latter be preserved from external influences. Foci of fat necrosis became visible to the naked eye three to five hours after the application of "pancreatin" and were found outside the abdominal cavity as early as twelve hours after intraperitoneal injection.

In considering the application of the results of experimental fat necrosis to the lesion as seen in man, it must be borne in mind that fat necrosis bears the same relation to obstruction of the pancreatic ducts as jaundice does to hepatic obstruction. Obstruction to the outflow of the pancreatic secretion causes its diffusion into the surrounding tissues (Opie). The escape of the ferment in the acute lesions of the pancreas is readily explained by obstruction or destruction of the finer ducts or by injury to the parenchyma. On the other hand either temporary or permanent obstruction of the duct of Wirsung by calculi or by cancer may be accompanied by fat necrosis. Usually other lesions exist as suppurative or chronic pancreatitis but in a few cases, as those reported by Fraenkel (stone in diverticulum) and by Flexner (stones in common duct) no lesion of the pancreas was found. There can be little doubt that in these cases the calculus causes compression of the pancreatic duct and an accumulation of secretion which finally becomes diffused into the adjacent tissues.

The following case would appear to belong in this group. A chronic atrophic cholecystitis with atrophy of the bile ducts and adhesions to head of pancreas apparently caused pressure upon the pancreatic duct.

Records of the Bender Laboratory, Autopsy No. 0.614. Autopsy by Dr. A. T. Laird, seven and one-half hours after death; female, aged forty-two.

Anatomical diagnosis: Extensive syphilitic ulceration of nose and palate, œdema of lungs, hydrothorax, chronic cholecystitis with almost complete obliteration of gall-bladder and ducts, fat necrosis of pancreas. The gall-bladder is greatly atrophied and lies in a mass of dense fibrous adhesions which bind it to the duodenum and the head of the pancreas, and which also surround and penetrate the foramen of Winslow. The cavity of the gall-bladder measures but two centimeters in diameter. The pancreas measures 17 x 4 x 2 centimeters. At its head, the capsule is much thickened by adhesions binding it to the gall-bladder and to the duodenum. Over its entire surface numerous greyish-yellow opaque areas, not extending into pancreatic tissue, are seen. The consistence of the pancreas is normal.

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Histological examination of the pancreas reveals numerous fat necroses, and dilated ducts filled with hyaline and granular material, desquamated cells and a few polymorphonuclear leucocytes. The latter also, to a moderate degree, infiltrate the walls of the larger ducts. No inflammation of the parenchyma proper is evident. The islands of Langerhans are unaltered.

The following accidental finding in a dog indicates that fat necrosis may follow a simple thickening of the orifice of the duct:

"Dog 84—weight 8650 gramms.—Isolated February 6th.—Urine normal on February 7th and 8th. Killed on February 12th for purpose of obtaining organs for injections in connection with cytolytic work. All organs normal except pancreas, the capsule of which is studded with numerous small greyish-yellow areas of definite outline and of firmer consistence than surrounding pancreatic tissue. No evidence of acute or chronic inflammation. No fat necroses of abdominal fat elsewhere. No obstruction of the duct is found. The papilla of duodenum, however, appears as a distinctly elevated, swollen, greyish-yellow ring; a sharp contrast to the normal appearance. A fine probe passes readily into the duct. The second pancreatic duct is not found. The orifice of bile duct, lying one and a half centimeters above pancreatic duct, can be located only by forcing bile from the gall-bladder. Histological examination shows fat necroses, chronic in character; pancreas otherwise normal."

Finally, as pointed out by Opie, we have fat necroses associated with cases of chronic intestitial pancreatitis in which duct obstruction by calculi is not present. Here it is probable that the newly formed fibrous tissues contracts about the smaller ducts, constricts them, and allows an accumulation of secretion which finally diffuses into the adjacent tissues. These necroses are most apt to be parapancreatic. I have found two examples of this condition in the autopsy reports of the Bender Laboratory; in one associated with localized chronic interstitial pancreatitis, in the other with atrophy and lipomatosis. Macroscopic evidence of duct obstruction did not exist. These reports are as follows:

No. 0.223. Autopsy twelve hours after death. Male, aged forty nine.

Anatomical diagnosis: Acute follicular duodenitis and ileitis; acute swelling of spleen and mesenteric lymph nodes; fatty degeneration of liver; arterio-sclerosis; atrophy of pancreas with lipomatosis, autodigestion and foci of fat necrosis; general infection with the bacillus of Friedländer. The *pancreas* appears to be of normal size, but much of the parenchyma is replaced by diffuse masses of fat tissue. On section small islands of pancreas are seen widely separated by fat tissue. This change is most marked at splenic end where little pancreatic tissue remains. The parenchyma in some areas is whiter

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and softer than normal, and in other places presents a reddish-brown appearance, suggesting minute hæmorrhages. On the surface and on section several, minute, opaque white points suggesting fat necrosis are seen. No calculi are found in the ducts; the vessels present a few small areas of atheroma.

Histological examination shows small islands of pancreas widely separated by adipose tissue, slight self-digestion of these areas, and typical foci of fat necrosis with minute hæmorrhages. The interlobular connective tissue is increased in amount; the small ducts dilated and some acini appear as duct-like spaces with flattened epithelium and contain a finely granular material. In some islands these altered acini are very abundant and apparently indicate atrophy from pressure within the lumen. The islands of Langerhans are unaltered.

No. 0.382. Autopsy ten hours after death. Male, aged sixty three.

Anatomical diagnosis: Arterio sclerosis, hypertrophy and dilatation of heart; general passive congestion; œdema; double hydrothorax; thrombus of right auricular appendage; multiple infarcts of lungs; fat necrosis of pancreas. *Pancreas* twenty centimeters long. Twelve centimeters from the tail, over an area two and a half centimeters in diameter, the capsule is greatly thickened; beneath the capsule the pancreas presents a congested area containing many small yellowish-white areas of soft cheese-like consistence. A few similar areas are found elsewhere in the pancreas.

Histological examination reveals a slight localized interlobular pancreatitis, with typical fat necrosis.

It is possible that the first of these cases belongs to the group described by Chiari, in which, in his opinion, self digestion of the pancreas occurs shortly before death as an agonal change and allows the escape of the fat splitting ferment and the development of fat necrosis with associated minute haemorrhages. That fat necroses may develop very quickly is shown in one of the experiments of the series carried out by Dr. Flexner and myself, in which necroses were evident eight hours after injection of a one per cent. solution of hydrochloric acid into the pancreatic duct. Wells has observed their occurrence three to five hours after the application of "pancreatin."

The theory that postmortem digestion of the pancreas may set free the pancreatic secretion and allow the development of fat necrosis has little evidence to support it. In connection with these agonal necroses Opie believes it is possible that shortly before death, owing to alterations in the character of the pancreatic juice, it may become thick and viscid, in consequence of which it flows slowly. Stagnation and slight diffusion of the secretion may result and cause the insignificant necroses occasionally seen.

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Reprinted from the ALBANY MEDICAL ANNALS, April 1904.

SYMPOSIUM ON DIABETES *

I. THE PATHOLOGY OF DIABETES.

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As it will be impossible in the short time at my disposal to cover all phases, many of them little understood, of the pathology of diabetes; and as the questions of chemistry and metabolism are to be discussed by Dr. Edsall who has specialized in these fields, I have determined to limit my remarks to a consideration of the pathology of that form of permanent diabetes, which, in the light of recent investigations, appears to be dependent upon lesion of the pancreas.

We may for the moment disregard the various forms of temporary glycosuria, variously known as alimentary, nervous, renal, and hepatic glycosuria and devote our attention to the permanent form, which, owing to its obscure etiology and the severe nutritional disturbances by which it is accompanied, the difficulties of treatment and the universally fatal termination has been the object of constant observation and investigation.

The literature of diabetes is replete with hypotheses and theories of the most divergent and conflicting character; but throughout this literature may be seen the tendency to associate diabetes with an altered physiology of the pancreas. This is due undoubtedly to the important function which this organ plays in the metabolism of carbohydrates, but also in no small degree to the frequency with which gross lesions of the pancreas are found in persons dying of the disease. Thus of the early English cases, Cawley† (1788), reports pancreatic calculus with atrophy of the gland; Bright (1833), cancer of the head of the pancreas with duct obstruction and

* Part of a Symposium on Diabetes, read before the New York State Medical Society at Albany, January 26, 1904.

† As the literature of diabetes has been so recently collected by Opie in his book, Diseases of the Pancreas, a work which has been freely used in the preparation of this summary, I have not attached a bibliography.

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consequent atrophy. The first definite statement of such a relation appears to be that of Bouchardat (1785), which received considerable support from both French and English writers. General support, however, was lacking, and the German medical world especially, did not concur until the publication of the convincing extirpation experiments of v. Mering and Minkowski. In these experiments it was found that complete removal of the pancreas is followed always by a definite diabetes of severe grade. Glycosuria appears as early as six hours after the operation; the sugar gradually increasing until the third day when it is usually about eight or ten per cent., though twenty-two per cent. (Hedon) has been observed. Towards the end, these high percentages fall, and as the sugar reaches its minimum, diacetic acid, acetone and oxybuturic acid appear in the urine. The other symptoms of diabetes are present, as hunger, thirst, and loss of weight. The animals ultimately succumb after varying periods of progressive emaciation and weakness. A repetition of these experiments upon a variety of animals has yielded uniformly concordant results. In birds glycosuria does not occur but the blood shows a considerable increase in its sugar content (hyperglycemia). Diet has but a slight modifying effect. While the maximum sugar elimination naturally occurs with a carbohydrate diet, an albuminous diet does not reduce it below five or six per cent., while fasting for seven days does not cause its entire disappearance. Moreover, it was found that if one-fourth or one-fifth of the pancreas was allowed to remain diabetes did not result; nor did it result, if after complete extirpation, a portion of the pancreas was transplanted subcutaneously. These experiments demonstrated conclusively a specific relation between some function of the pancreas and carbohydrate metabolism. What this function might be, or what changes in the pancreas might disturb its equilibrium was not clear. It was evident, however, that it could be explained only by an internal secretion, for no disturbance followed ligation of the duct. Furthermore it was evident that no other organ could vicariously assume this function of the pancreas.

Stimulated by these experiments, interest in the pancreas was renewed and as a result much data concerning the pathology of the pancreas of diabetes came to hand. Seegen, Hansemann, Dieckhoff and Williamson reported the results of large series of cases. In these, as well as in those previ-

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ously reported by Windle, Frerichs and White, definite lesions of the pancreas occurred in a very large proportion of the cases. This relation is strikingly shown in the tabulations of Oser. Calculus of the duct with secondary atrophy stands out as a prominent condition. Cancer of the head with like atrophy was not uncommon. In Hansemann's series simple atrophy was present in thirty-six of forty cases. Other conditions found were chronic pancreatitis and lipomatosis.

Still many cases of diabetes constantly came to notice without lesion of the pancreas. Naunyn, indeed, in a series of forty autopsies found only one case in which the disease could be ascribed to disease of the pancreas. On the other hand, many cases of grave disease of the pancreas without diabetes were observed; Hansemann reports such a case in which complete destruction of the pancreas existed. This anomalous condition he attempts to explain by the hypothesis that in primary cancer of the pancreas the cells of the new growth retain, in part at least, the function of the cells from which they are derived and that therefore the internal secretion is not disturbed.

At the same time various attempts were made to associate with diabetes some distinct histological picture; as the combined chronic pancreatitis and arterio-sclerosis of Hoppe-Seyler and Fleiner, and the perivascular sclerosis of Lemoine and Lannois. An important condition observed by the latter was the penetration of the fibrous strands into the acini, thus separating the cells and presenting a condition which they designated unicellular sclerosis. Hansemann particularly associated with diabetes a condition of the pancreas which he calls granular atrophy but which from his description appears to be a primary chronic pancreatitis with atrophy.

The most important contributions to the histology of the pancreas of diabetes are those made during the past few years by Opie. He distinguishes two forms of chronic pancreatitis; (1) interlobular pancreatitis, characterized by the formation of fibrous tissue between the lobules, which are often invaded from the periphery and (2) interacinar pancreatitis, in which the newly formed fibrous tissue is diffusely distributed within the lobule, separating the acini and invading the islands of Langerhans. With the first type, frequently associated with duct obstruction, diabetes occurs only in those relatively uncommon cases in which an advanced

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sclerosis involves the islands. With the interacinar type, however, diabetes is much more frequent. Another important change observed by the same writer is a hyaline transformation of the islands with little or no alteration of the secreting parenchyma. He therefore looks upon involvement of the islands of Langerhans as the important point in the pathology of diabetes. His figures support this view; in twenty-one cases of interlobular pancreatitis, diabetes occurred but once and in this case the advanced sclerosis had produced alterations of the islands; while in seven of nine cases of the interacinar type, diabetes coexisted; and in six of nineteen cases of diabetes, hyaline transformation of the islands was present.

Such observations imply that the islands are in some way concerned in carbohydrate metabolism and therefore of fundamental importance in any consideration of the etiology of diabetes. The occurrence of these lesions in diabetes has been confirmed by Weichselbaum and Stangl, Herzog, Gentes, Wright and Joslin, Curtis[1], Finney[2], Schmidt, Hansemann and Herxheimer[3]. The last three writers, however, are not prepared to admit that these changes are of etiological importance.

In this connection the following notes of five cases of diabetes and one of acute glycosuria, studied during the past two years, may be of interest:

I. Records of the Pathological Laboratory, University of Pennsylvania, Autopsy No. 01.212. Female, aged sixty-two years. *Clinical diagnosis*—Diabetes, moist gangrene of leg, tetanus. *Anatomical diagnosis*—Thrombosis of left iliac artery and its branches; softened thrombi in left auricular appendix; moist emphysematous gangrene of left leg; infarction of spleen and left kidney; chronic obliterative pericarditis; chronic mitral endocarditis; hypertrophy of left ventricle; chronic diffuse nephritis; chronic interstitial pancreatitis; chronic adhesive pleuritis. *Histological examination*—Interacinar pancreatitis with involvement of many of the islands of Langerhans by the invasion of dense bands of fibrous tissue.

II. Records of the Pathological Laboratory, University of Pennsylvania, Autopsy No. 01.309. Male, twenty-seven years. (Service of Dr. J. H. Musser, University Hospital.) *Clinical diagnosis*—Phthisis pulmonalis, diabetes mellitus, Banti's disease. History of diabetes of two years' duration; sugar varied in amount from 1.25 to 7.5 per cent.; specific gravity of urine 1028 to 1040. *Anatomical diagnosis*—Splenomegaly; slight chronic interstitial hepatitis; general tuberculous peritonitis; tuberculosis of lung (caseous and gelatinous pneumonia with cavity formation); tuberculous

1. *L'Echo Med. du Nord*, 1902, vi, 140.
2. *The Medical Chronicle*, 1903, v, 137.
3. *Orth-Festschrift*, 1903, s. 38.

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pleuritis; slight chronic mitral endocarditis; fatty degeneration of heart and kidneys. *Pancreas*—The surface is more nodular than normal, the depressed portions œdematous. On section the nodular appearance is very marked. The consistence is about that of the normal pancreas. *Histological examination* reveals a moderate perivascular fibrosis and a hyaline degeneration of many of the islands; approximately one of every five is hyaline.

III.—Records of the Pathological Laboratory, University of Pennsylvania, Autopsy 02.16. Male, aged thirty-eight years. (Service of Dr. Alfred Stengel, University Hospital.) *Clinical diagnosis*—Diabetes, tuberculosis. *Anatomical diagnosis*—Gangrene and multiple abscesses of lungs; acute fibrinous pleuritis; fatty degeneration of heart and liver; cloudy swelling of kidneys; slight atrophy of thyroid gland; chronic interstitial pancreatitis; fibrosis and caseation of right adrenal; arterio-sclerosis; acute splenic tumor; multiple superficial erosions of the œsophagus. *Pancreas*—Weight seventy grammes, smaller than normal and firmer. The shape is more distinctly triangular than usual. The surface of the pancreas is grossly nodular. *Histological examination* of the pancreas reveals a slight diffuse increase of connective tissue; the islands of Langerhans are normal. The right adrenal is almost completely destroyed by tuberculous caseation and newly formed fibrous tissue. A small ganglion adjacent to the adrenal is not involved in this process. Left adrenal is normal. The alveoli of thyroid gland are moderately dilated.

IV.—Case of Dr. Wm. Pepper, of Philadelphia, presenting a history of nephritis, uræmia and acute (terminal) glycosuria. The autopsy report is not available. For sections of the pancreas and for the laboratory report which latter, owing to the peculiar terminal character of the glycosuria is given in full, I am indebted to Dr. Pepper. *Clinical history*—Female, aged fifty-eight, admitted to the University Hospital, September 4, 1902. "Patient in a semi-delirious condition and cannot give a satisfactory history of herself. From her daughter it was learned that the patient had been complaining of headache, dizziness and defective vision for the last two weeks, and that during the past week she has been at times quite delirious. On admission catheterized; urine slightly cloudy, dark amber; no precipitate; specific gravity 1025; albumen 1-15 by bulk (centrifugated); *no sugar;* no bile, indican negative; diazo not made; a few flat round epithelial cells, a few pale and dark granular casts, and a few white blood cells. *Sept. 5th*—Mental condition better. Bowels moved freely. Urine dark amber; slightly cloudy; very light flocculent precipitate; specific gravity 1030; distinctly acid; albumen 1-15 by bulk (centrifugated); *no sugar;* bile and indican negative; a few flat and round epithelial cells, few white blood cells, many pale and dark granular casts. *Sept 6th—Blood*—Hæmoglobin, eighty-nine per cent.; red cells 5,010,000; white cells 10,860; Widal negative; no malaria parasites; nothing abnormal in stained films. Urine 9 A. M. dark amber; slightly cloudy; light, flocculent precipitate; specific gravity 1029; distinctly acid; albumen 1-15 by bulk (centrifugated); *no sugar;* bile and indican negative. Many flat and round epithelial cells, a good many white blood cells, very many very short, pale and dark granular casts, a few waxy casts. 5 P. M. urine color changed to a very pale amber; slightly cloudy; no precipitate; specific gravity 1029; distinctly acid; a

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decided trace of albumen; *sugar* 0.83 per cent. by Fehling's test; bile and indican negative; sediment shows many short pale and dark granular casts, a few waxy casts, very many flat round and spindle epithelial cells, very many white blood cells, many mixed urates. *Sept. 7th*—Urine 11 A. M. pale amber, slightly cloudy; light flocculent precipitate; specific gravity 1031; distinctly acid; decided trace of albumen; *sugar* 0.83 per cent.; bile and indican negative. Many short pale and dark granular casts, few waxy casts, many flat spindle and round epithelial cells, many white blood corpuscles, many mixed urates. *Sept. 8th*—Urine 2 P. M. pale amber; hazy; specific gravity 1030; acid; *sugar* present in large quantities; decided trace of albumen; epithelial cells, urates, no casts. *Histological examination*—of the pancreas shows irregular foci of slight interacinar pancreatitis with distinct involvement of the islands of Langerhans. The islands are frequently enlarged; the fibrous tissue abundant and often somewhat hyaline in appearance; the cells compressed and indistinctly outlined.

V—*Bender Laboratory Records, Autopsy 0.726.* Case of Dr. Andrew MacFarlane, Albany, N. Y. *Clinical abstract*—Male, aged twenty-six; laborer, duration of diabetes about eight months. Sugar constantly present in urine rising at times as high as four per cent.; diacetic acid and acetone also present. *Autopsy*—The abdominal viscera only were examined through a limited incision. *Pancreas*—Apparently normal in its gross appearance. *Histologically,* scattered areas of interacinar pancreatitis are found. The islands present a slight but definite increase of connective tissue with moderate atrophy of the intervening cells. A few small areas of fat necrosis exist.

VI—Records of the Pathological Institute, University of Leipzig, Autopsy 98 (1898).* Female, aged twenty-six years. *Clinical diagnosis*—Diabetes, pneumonia. *Note of post-mortem examination*—Extreme sclerosis and atrophy of the pancreas with presence of calculi (weight of pancreas, fifty-four grammes); diffuse lobular pneumonia with fibrinous pleuritis; hydro-pericardium; cloudy swelling of liver; fatty degeneration of kidney; calcareous bronchial lymph nodes. *Histology of pancreas*—Extensive atrophy and chronic pancreatitis of the interlobular type. In the more sclerotic portions the growth of connective tissue is interacinar. The islands are few in number, small, often isolated and frequently invaded by fibrous strands.

Lesions of the islands occurred in five of these six cases; in one the change was of the nature of a hyaline transformation; in the other four an interacinar pancreatitis with involvement of the islands existed. Whether or not the glycosuria in case III, in which the pancreas was normal, was dependent upon the lesion of the adrenal it is impossible to say. Glycosuria does not usually accompany such lesions. On the other hand the experiments of Blum, Herter and Richards indicate that the adrenal is in some way concerned in carbohydrate metabolism. These investigators found that

* For the privilege of reporting this case, I am indebted to Prof. F. Marchand of the University of Leipzig.

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after the injection into animals of the adrenal gland or adrenal extract, a temporary glycosuria results. Herter and Richards produced the same result by painting the surface of the pancreas with the extract. These experiments, however, are not analogous to destruction of the adrenal.

I can at this time also give a preliminary report of an investigation, as yet incomplete, of the diabetes associated with cancer of the pancreas. It is well known that cancer of the pancreas may or may not be accompanied by glycosuria. We have no definite explanation of the condition under which it occurs, though a resume of the literature shows that it is most common when the tumor is in the head of the pancreas and by duct obstruction causes atrophy (chronic pancreatitis) of the distal portion of the organ. The reverse condition, complete destruction of the gland by cancer without diabetes, is likewise difficult of explanation. It is true that Hansemann has suggested that the function of internal secretion is preserved by the cells of the new growth; but this is not applicable to secondary tumors and if we accept the theory that the islands alone furnish the internal secretion it is not tenable, as pointed out by Ssobolew and Opie, unless we assume that all primary tumors of the pancreas have their origin in the islands, and in support of this last possibility there is little evidence. Nicholls[4] has reported a primary adenoma of an islands, and Fabozzi[5] has recently described several primary cancers of the pancreas which he believes to have arisen from a like source. Fabozzi's observations, however, are not conclusive and are entirely opposed to the great mass of work on this subject.

I have been able to collect for study thirty cancers of the pancreas. Three of these were accompanied by glycosuria, which in one case was a true diabetes, and in the second an intermittent glycosuria. I have no data concerning the character of the glycosuria in the third case. In the first case the tumor was in the head of the pancreas, causing obstruction of the duct with chronic pancreatitis of the distal portion of the organ. This chronic inflammation was for the most part interlobular, but in places was of the interacinar type with involvement of the islands, that is, presented the lesion which, according to our new ideas is supposed to be essential to the occurrence of diabetes. The third case was

4. *Journal of Medical Research*, 1902, viii, 385.

5. *Ziegler's Beitrage*, 1903, xxxiv., 199.

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unsatisfactory for study inasmuch as only the tumor had been preserved and observations concerning the condition of the uninvolved pancreas could not be made. In the second case, accompanied by intermittent glycosuria, the pancreas showed no noteworthy change in the uninvolved portion of the organ. This case, similar to those reported by Wille, brings up the vexed question of alimentary glycosuria. It is known that a normal individual may digest without disturbance from 150 to 250 grammes of sugar, but that an increase over this amount may lead to temporary excretion of glucose in the urine. This excretion is due to hyperglycemia, the inevitable result of a sudden flooding of the circulation with an amount of glucose beyond that which the body is able at once to consume. On the other hand, in a number of abnormal conditions where there is no actual diabetes, an alimentary glycosuria may be produced by an amount of sugar which in the economy of the normal individual is easily consumed. Among the prominent conditions in which this occurs may be mentioned neuroses (traumatic and other forms), organic nervous diseases, alcoholism, infectious diseases, exophthalmic goitre, hepatic and pancreatic disease. Is it not possible that this temporary excretion of sugar is due to some transient disturbance of the function of the islands brought about by vascular disturbances of the islands or by some toxic substance, perhaps of the nature of an autotoxin, affecting the secretion of these structures or temporarily throwing them out of function? In a destructive disease of the pancreas, as cancer, a certain number of the islands are necessarily destroyed; the remainder, however, may be sufficient under normal circumstances to furnish the necessary secretion, whatever it may be, essential to carbohydrate metabolism; but if overtaxed by an unusual ingestion of glucose, hyperglycemia and a consequent, glycosuria might result. This explanation has occurred to me in connection with my case of cancer accompanied by intermittent glycosuria and that it is not entirely hypothetical is indicated by the observations of Ssobolew, confirmed by Herzog, that in some cases of permanent diabetes the pancreas exhibits a great diminution in the number of islands and in some cases an entire disappearance.

This functional deficiency, however, is far from proven, and in mentioning it I do not wish to be placed in the position of advocating pancreatic origin for all forms of

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diabetes. We have a definite basis for ascribing a certain portion of the cases of diabetes to lesions of the pancreas; but here we must rest until an increase in our knowledge allows further conclusions. It is probable as suggested by Naunyn that with the pancreas other organs preside over carbohydrate metabolism, though perhaps in a less degree, and that the pancreas may act vicariously for them, although their function may not be sufficient to be substituted for that of the pancreas.

Another point brought out by this investigation of cancer of the pancreas is the resistance of the islands to invasion or obliteration by the new growth and the accompanying sclerotizing inflammation. Numerous unaltered islands were frequently seen in the fibrous tissue at the margin of the growth where the acini had been completely destroyed; moreover, these structures, both at the edge of the tumor and in distant portions of the organ, were often three to five times larger than normal. This persistence indicates the resistance of the islands and the increase in size suggests a hypertrophy possibly compensatory in character. No cases of complete involvement of the organ by cancer similar to those of Litten and Hansemann were seen; in the few instances of extensive invasion a sufficient amount of the organ, by analogy with the partial extirpation of v. Mering and Minkowski, remained to carry on the internal function of the gland.

Whatever the ultimate explanation of diabetes may be, it must be admitted that our knowledge of pancreatic diabetes has been largely extended by the recent studies of the islands of Langerhans. And here it may be pertinent to inquire what evidence have we that the islands from their anatomy, development and appearance in diseases other than diabetes are independent structures concerned in carbohydrate metabolism.

From the discovery of these structures by Langerhans in 1869, until within a few years, many and varied efforts have been made to explain their origin and function. They have been regarded from time to time as nervous elements, primary ducts, embryonic remains and as immature or wasted acini. The study of the ductless glands is largely responsible for the recognition of the similarity of structure of the islands and these organs. The structure of the islands—columns of cells rich in protoplasm, lying in an abundant vascular network of a sinusoidal character and with no excretory duct—

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naturally suggests as their function the elaboration of some substance destined to be introduced into the circulation. This theory of the independence of the islands, first advanced by Shäfer, received considerable support from the experiments of Ssobolew. He found that after feeding animals on carbohydrates the islands became granular, indicating, according to his interpretation, a greater functional activity due to the increased demand for a ferment essential to carbohydrate metabolism. Furthermore he found that in the sclerotic atrophy following ligation of the ducts in animals the islands are not implicated and glycosuria does not result. These observations have been confirmed by Schulze. A similar persistence is frequently seen in the human pancreas in the sclerosis following duct obstruction; and has also been observed by Schlesinger, Opie, Condon[6] and myself[7] in the peculiar fibrous induration of the organ which occurs, not infrequently, in congenital syphilis.

Again, in the embryonic development of the islands we have evidence that they are destined for some special function. As I have recently demonstrated[8], the islands at an early stage of the growth of the pancreas arise from the primary acini and for some time remain connected to these structures by a solid process of cells; but eventually become entirely separated, and with the development of a blood supply proportionally greater than that of the acinus, become anatomically independent. Such anatomical differentiation argues for a special function, and taking into consideration the recently accumulated knowledge, the result of pathological investigation, we are forced to the conclusion that this function is an internal secretion concerned in carbohydrate metabolism and therefore of fundamental importance in any consideration of diabetes. This, however, is not equivalent to saying that all forms of diabetes may be traced to functional or structural changes of these structures. Fully one-half of the reported cases studied with regard to lesions of the islands show no alteration of these structures. That several forms of diabetes exist and that other organs than the pancreas are concerned in their etiology is evident; but this does not detract from the value of our recently acquired knowledge of pancreatic diabetes. The manner in which the

6. *Trans. Chicago Path. Society*, 1899-'01, IV., 200.

7. *American Medicine*, 1903, VI, 1020.

8. *American Journal of Anatomy*, 1903, II, 445.

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hypothetical internal secretion of the islands is supposed to act comes under the head of chemistry and metabolism and will doubtless be considered by Dr. Edsall.

A consideration of diabetes would be incomplete without a consideration of the forms of glycosuria apparently dependent upon changes in organs other than the pancreas. As little however has been added in recent years to our knowledge of these conditions, I will speak of them but briefly. The forms of glycosuria associated with acromegaly, with cirrhosis of the liver, with arterio-sclerosis, and especially the diabetes of hæmochromatosis, in the light of recent investigations would appear to have a relation to disease of the pancreas.

Thus in acromegaly chronic inflammation of the pancreas has frequently been found at autopsy and it is probable as suggested by Opie, that "induration presumably analogous to that which acromegaly causes elsewhere occurs also in the pancreas and where sufficiently advanced produces glycosuria or even permanent diabetes."

The frequency with which arterio-sclerosis is associated with diabetes renders it probable that this condition by affecting the nutrition of the pancreas may be the cause of changes, inflammatory or sclerotic in nature, leading eventually to diabetes.

That the diabetes accompanying cirrhosis of the liver may, in many cases, be due to a coincident chronic pancreatitis, the result of a common etiological agent is indicated by the studies of Lefas, Opie and Steinhaus[9]. A more striking example of the dependence of chronic lesions of the liver and the pancreas upon a common etiological factor is hæmochromatosis (*diabète bronzé*). This condition, first described by v. Recklinghausen, is characterized by the extensive deposition of an iron-containing pigment in the cells of various organs and tissues, and is associated with a necrosis of the parenchymatous cells and a proliferation of the stroma. The liver and pancreas suffer most, the former being the seat of a hypertrophic cirrhosis, the latter of a chronic pancreatitis. The diabetes occurring in this condition has been explained by some writers as the result of the blood destruction, by others as the result of the pancreas lesion. Opie, in one case, found the inflammation to be of the intracinar type with involvement of the islands of Langerhans; and therefore concludes that this lesion is responsible for the occurrence of diabetes. In his case,

9. *Deutsch. Arch. f. klin. Med.* 1903, lxxiv.

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however, diabetes did not exist owing to the incomplete destruction of the islands; the patient dying of typhoid fever before the disease had reached its height.

It is well established that glycosuria, temporary or otherwise, may follow lesions of the central nervous system and perhaps also of the sympathetic and larger peripheral nerves. Claude Bernard's classical *piqûre* of the floor of the fourth ventricle in animals, lesions (haemorrhage, tumor and softening) of the same location (medulla) and various pathological changes of the brain and cord in man illustrate this relation. We have, however, no definite information and Naunyn's theory that through the secretory or nutritive nerves we have a disturbance of function in the organs presiding over carbohydrate metabolism, is as satisfactory as any other.

In experimental phloridzin diabetes it has been demonstrated that a true hyperglycemia does not exist and that the glycosuria is due to an injury of the renal epithelium which allows an escape of the sugar normally present in the blood. An analogous condition (renal diabetes) in man has been suspected but not proven.

The influence of the adrenal gland upon carbohydrate metabolism has already been mentioned.

The relation of the thyroid gland to glycosuria is unexplained. Hansemann has collected fifteen cases in which diabetes and exophthalmic goitre were associated. Alimentary glycosuria is also frequently seen in this condition, according to Chvostek in sixty-nine per cent. of all cases; and it has also been observed after the therapeutic use of thyroid extract. It is worthy of note, however, that in none of the cases of diabetes associated with exophthalmic goitre has the condition of the pancreas been studied (Opie).

I have attempted to place before you in this brief summary the relation of the pancreas and especially the islands of Langerhans to diabetes. If I have dwelt too strongly upon this point it is because the knowledge of this relation enables us to sharply separate at least one form of diabetes from all others, and thus offers a definite point of departure for the study of those forms of glycosuria which, from our knowledge of the complexity of carbohydrate metabolism, we assume may be due to disturbances of other organs.

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NOTE

THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1904-'5. These have appeared in various medical journals, but for the sake of uniformity in paper and press work, the reprints have been taken from the Albany Medical Annals. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *January*, 1906.

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Reprinted from ALBANY MEDICAL ANNALS, February 1906.

EXPERIMENTAL CIRRHOSIS OF THE LIVER.*

BY RICHARD M. PEARCE, M. D.

(From the Bender Laboratory, Albany, N. Y.)

(Plate III.)

The experimental studies upon which this communication is based were suggested by an investigation[1] of the necroses occurring in the liver of the dog as the result of the intravenous injection of haemolytic immune sera. These necrotic lesions, which appear to have a very definite relation to thrombi composed of fused red blood corpuscles, vary in position and extent according to the amount of serum administered. Small doses cause focal lesions more or less isolated and irregularly distributed; large doses produce a diffuse necrosis which spares only the tissue about the larger portal spaces. The uniformity and extent of this latter lesion suggested the importance of studying the repair process which naturally follows it in those animals surviving the acute toxic effects of the serum. It was evident that the extent of the injury was such as to preclude complete repair by the regeneration of liver cells alone. If then, the defect were to be repaired by connective tissue proliferation the resulting histological picture would, except for a difference in the distribution of the new tissue, closely resemble cirrhosis in man.

Experiments based on this method have not, heretofore, been made. Joannovics,[2] alone, of the few investigators who have studied the lesions of the liver due to haemolytic sera, has described repair about foci of necrosis. Flexner,[3] in 1894, while studying the lesions occurring in the organs of the rabbit after the injection of dog's serum observed a well marked cirrhosis due apparently to repair about multiple necroses. The lesion was found, however, but once and could not be reproduced in other animals. The literature contains, as far as I am aware, no other references to similar lesions due to serum injections.

Methods.—Dogs were injected either in the smaller branches of the femoral vein or in the abdominal cavity with serum obtained from rabbits which had received repeated injections of

* This study has been conducted under a grant from the Rockefeller Institute for Medical Research. Read before the American Association of Pathologists and Bacteriologists, Chicago, April 19, 1905. Published also in *The Journal of Experimental Medicine*, 1906, viii, 64.

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the red blood corpuscles of the dog. The dose usually employed was one cubic centimetre of serum to 500 to 1000 grammes of body weight. The majority of the animals died within forty-eight hours; those which survived were killed at intervals varying from forty-eight hours to thirty-six days.

Character of the Primary Necrosis.—The necrotic lesions in the liver vary according to the dose of the serum. As the etiology and the general character of the focal necroses have been discussed elsewhere, only the more extensive form of necrosis, which, through an equally wide-spread process of repair leads to cirrhosis, will be considered at this time. The macroscopic appearance of the liver in animals dying within a few minutes or hours after injection is that of intense congestion. Microscopically, the vessels are found to be distended by closely massed red blood corpuscles. The coalescence of red cells is very evident in the portal veins; while in the capillaries the occlusion leads to a distension so great that the columns of liver cells are more or less obscured. This congestion is less evident about the larger portal spaces. After twenty-four to forty-eight hours, the liver presents a uniformly mottled appearance; fine irregular yellowish brown or greyish yellow non-elevated areas being sharply separated from deeply congested or occasionally even haemorrhagic areas. On section the brownish portions have a distinct hyaline appearance. The superficial portions of the liver are uniformly more extensively involved than are the deeper portions though in some of the smaller lobes the necrosis may be quite general. Histologically, the necrosis, which is hyaline in character, involves all portions of the liver tissue except circular areas of varying size in the immediate neighborhood of the larger portal spaces (see Fig. 1).

In the necrotic areas the destruction, as far as the hepatic cells are concerned, is uniform and complete; the cells of the capillaries may, however, persist. A narrow ring of liver cells with vacuolated protoplasm and pyknotic nuclei separates, as a rule, the necrotic from the normal tissue. Leucocytic infiltration may or may not be present. The capillaries of the necrotic tissue are widely dilated and tightly packed with swollen and distorted red blood corpuscles which may occur in masses or may retain distinct outlines. In the congested portal veins on the other hand the fusion is quite constant, the plugs for the most part having a distinctly hyaline appearance. The perivascular spaces

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of the capillaries are distended with serum and the bile passages of all sizes are, as a rule, dilated and engorged with bile.

The cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal vein by fused masses of red cells. To the effect of this obstruction, essentially a thrombosis, is added the pressure exerted by the perivascular oedema and the over-filled bile capillaries. In portions of the liver midway between the larger portal spaces these factors are sufficient to overcome the pressure in the capillaries from the hepatic artery and necrosis results; the cells in the neighborhood of the larger portal spaces, on the other hand, are preserved through a better supply dependent, presumably, upon the greater arterial pressure in this region.

A review of the literature of infarction of the liver in man and of experimental infarction shows no condition analagous to that here described; nor are any of the theories put forth concerning the etiology of infarction applicable to it. A possible exception is the wide-spread haemorrhagic infarction produced by Wooldridge[4] as the result of injecting into the jugular vein of the dog a complex proteid substance derived from the thymus and other glandular organs. The infarctions were associated with thrombi in the branches of the portal vein and in this regard as well as in the character of the necrosis, Wooldridge's lesion resembles that just described. Moreover, in animals which survived fourteen days, he observed scattered foci of repair resembling early cirrhosis. He does not consider the thrombosis alone to be sufficient cause for the necrosis, but believes that an important adjuvant is some change in the chemical composition of the blood caused by the proteid substance injected.

*The Reparative Process.**—Only fifteen of forty-three animals survived the acute effects of the serum a sufficient length of time to allow repair of the liver lesion to take place. The liver of each, however, shows some stage of repair, and as various periods from thirty-eight hours to thirty-six days are represented, it has been possible to study all stages of the development of the cirrhotic lesion.

At thirty hours the first and only evidence of repair is karyokinesis of the liver cells. This, however, is not conspicuous and

* Only a general outline of the reparative process will be given at this time; the details of the finer changes and their interpretation will be presented in a future communicaton on the repair of liver tissue.

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the mitotic figures are found only after prolonged search. They occur, uniformly, not at the edge of the necrotic tissue, but in liver cells two or three rows removed. Mitotic figures have never been seen earlier than thirty-eight hours, and at this period in but one animal.

The period from forty-eight to sixty hours is represented by five animals. The character of the repair is the same in all, but some difference in degree is evident. The most striking feature is the proliferation of the endothelial cells. These surround the necrotic tissue and penetrate it from every side. Similar cells corresponding to the remains of the capillaries may be seen in some places within the necrotic areas. Many of these cells have irregular nuclei suggestive of mitosis, but a definite karyokinetic figure, in a cell surely endothelial, was found at this stage but once; and this was in the liver of an animal killed exactly forty-eight hours after injection. The endothelial cells show a tendency to surround small fragments of necrotic liver cells and occasionally they contain one or two red blood corpuscles. Leucocytic infiltration occurs to a very slight extent.

By the end of the fourth day the proliferation has advanced so rapidly that the bulk of the necrotic tissue has been replaced. Within the necrotic areas the bands of new tissue are more definite. Mitotic figures in liver cells are so numerous that three or four may be found in one field of a one-twelfth lens. A few lymphoid cells are seen in the portal spaces.

The picture at the fifth day differs only in the extent of the process. The new tissue has assumed all the characteristics of granulation tissue and contains giant cells which surround fragments of hyaline material. The first suggestion of intercellular fibrillæ is seen at this stage.

The later stages from the eleventh to the thirty-sixth day illustrate the gradual transformation of this young granulation tissue into a very definite connective tissue. At the eleventh day the new blood vessels are very prominent and the fibrillated character of the connective tissue well marked. All stages after the fourth day show a few scattered lymphoid cells, but this has not been a prominent feature except in one animal, killed on the twenty-fifth day, in which the tissues of the portal spaces were filled with lymphoid and plasma cells.

The oldest as well as the most typical lesion was that found in an animal killed on the thirty-sixth day (see Fig. 2). Micro-

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scopically, the liver was much firmer than normal, had a finely granular surface, and was deeply bile stained. The capsule showed irregular areas of thickening and was mottled by an ill-defined congestion. On section a distinct pseudo-lobulation was evident; definite islands of brownish yellow liver tissue being marked off by a fine greyish network of newly-formed tissue. Histological examination shows broad bands of connective tissue entirely replacing the necrotic areas and forming a uniformly arranged network separating the surviving islands of liver tissue about the larger portal spaces. The new tissue is distinctly fibrous and contains many newly formed blood vessels and bile ducts; it stains deeply by Mallory's connective tissue method. The formation of new liver cells is still demonstrable. Fragments of necrotic hyaline cells, not infrequently partially calcified, are found in the midst of the new connective tissue. Large irregular multi-nucleated masses of protoplasm surround these and are apparently active in englobing and removing them. These multi-nucleated cells, essentially foreign body giant cells, are derived in part from endothelial cells and in part from liver cells. Associated with them are numerous multinucleated liver cells without inclusions. Lymphoid and plasma cells are present, but only in small numbers.

Discussion.—The final stage of the lesion herein described, constituting as it does a chronic interstitial hepatitis of diffuse, but uniform distribution, may justly be termed an experimental cirrhosis. No close analogy, however, can be drawn between it and human cirrhosis, for, with the possible exception of the so-called central cirrhosis associated with chronic passive congestion, a form of interstitial hepatitis with similar distribution of the new tissue does not occur in man. In this connection Bostreom's[6] recent discussion of liver cirrhosis as a repair process in chronic passive congestion is of especial interest. As the result of a study of material from man he reaches the conclusion that the congestion causes destruction of liver cells not necessarily by pressure of the widened capillaries, but through nutritive and functional disturbances. With these conditions are associated rupture of the capillary wall and the escape of red cells into the perivascular lymph spaces. Thrombosis also is not an infrequent occurrence and has a close relation to the destruction of liver cells. The repair, which is most active in the region of the portal spaces, results in a very definite cirrhosis. When one considers that the

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necrosis in my experimental lesion is preceded by an intense congestion associated with all the etiological factors described by Bostroem, the analogy of the repair lesion to the cirrhosis which he describes becomes very apparent. Comparisons as to the etiology of cirrhosis in general are not justifiable, for we know of no toxic substances associated with abnormal conditions in man which are capable of causing the wide-spread necrosis seen in these experimental lesions. The only condition comparable is acute yellow atrophy with which the early necrotic and reparative lesions of the second to the sixth day have much in common.

On the other hand, however, these experimental lesions demonstrate that a cirrhosis may follow extensive primary destructive lesions and thus support the theory of Kretz[6] that cirrhosis is essentially a reparative process. Kretz, who bases his conclusions on an extensive study of the disease in man, believes cirrhosis to be the result of successive processes of repair following repeated focal injuries of the liver parenchyma. The primary lesion is, he thinks, a destruction of groups of liver cells at the periphery of the lobule. After such destruction the uninjured cells of the lobule, as well as the cells of the bile ducts, proliferate in an attempt to repair the injury. The continued occurrence of degeneration and regeneration causes the formation of new connective tissue which eventually atrophies thus leading to the picture seen at autopsy. Cirrhosis, therefore, is the result of repeated localized destructive lesions from which the liver has more or less recovered. This view it will readily be seen accepts Weigert's[7] opinion that the primary lesion in all interstitial new growth of tissue is cell death and also includes Kirikow's[8] opinion that in addition to cell death the continual action of the toxic substance is necessary; but adds the important factor of continuous regeneration.

W. G. MacCallum's[9] study of the regenerative changes in human cirrhosis strongly supports the theory of Kretz as do also the studies by McPhedran and A. B. MacCallum,[10] Meders,[11] Marchand,[12] Stroebe,[13] Barbacci,[14] W. G. MacCallum[15] and others of repair in acute yellow atrophy of the liver.

The experimental studies of repair after various mechanical injuries also indicates the ease and rapidity with which liver parenchyma repairs loss of substance. From the observations of Podwyssozki[16] and Ponfick,[17] it is seen that slight injuries are

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repaired by the proliferation of either liver cells or the smaller bile ducts; connective tissue repair occurring only when loss of substances exists. Of special interest is the true hyperplasia observed by Ponfick and by v. Meister[18] after extirpation of large portions (one-quarter to three-quarters) of the entire liver.

On the other hand the argument is presented that focal necrotic lesions of the liver frequently occur in man without repair either by proliferation of parenchymatous cells or by formation of connective tissue. In this connection the liver lesions of typhoid fever, diphtheria and other acute infections as well as various experimental infections of animals are quoted. It is probable, however, that in such cases the reparative power of the cells is in some way delayed, or consists possibly of a true regeneration of liver cells without the proliferation of connective tissue; for in hog cholera, in which above all other diseases, necroses of the liver are most abundant and widespread, cirrhosis of the liver commonly occurs. Salmon, Smith and Kilborne,[19] in the study of hog cholera in an epidemic including both acute and chronic cases, found well marked cirrhosis in about half of the animals examined.

The question as to whether the interstitial tissue or the parenchyma is primarily affected in cirrhosis receives little enlightenment from the literature of experimental cirrhosis. Heukelom,[20] who reviewed the literature up to 1896, collected nineteen different methods said to be capable of producing cirrhosis and to these Joannovics[21] in a recent summary adds others. None, however, produce a lesion analagous to that occurring in man. These methods may readily be divided into two groups. In the first we have procedures essentially mechanical in nature, as ligation of the ducts or vessels of the liver, the injection of irritating substances into the ducts or directly into the liver substance, and their application to its surface. The second group includes the administration by the mouth, or by subcutaneous or intravenous injection, of various toxic substances. As a general rule the mechanical methods lead to a more or less irregular connective tissue formation, sometimes with considerable sclerosis, but the lesion under these circumstances is more of an atrophy than a cirrhosis. The toxic agents, for which positive results have been claimed, have been introduced so that they reach the liver through the blood stream. The lesion attributed to such substances is usually described as a primary degeneration

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of the liver cells with a slight increase of connective tissue, limited as a rule, to the portal spaces; in a few instances a definite perilobular growth of connective tissue, independent of parenchymatous degeneration, has been described. Few of these lesions, however, even in their final stages are comparable to the cirrhosis of man and in none has it been possible to follow step by step the development of a lesion which could probably be termed an experimental cirrhosis.

Summary.—The reparative process which follows the widespread necrosis of the dog's liver caused by the injection of hæmagglutinative serum constitutes a chronic interstitial hepatitis of definite and constant character. This is not only a new type of experimental liver lesion, but is more definitely a cirrhosis than is any other experimental lesion hitherto described. It is of importance in explaining the histogenesis of cirrhosis, and incidentally various repair processes in the liver; but does not aid in the elucidation of the etiology of cirrhosis in man, nor does it explain the peculiar arrangement of the new connective tissue in any form of human cirrhosis except, possibly that associated with chronic passive congestion. It definitely demonstrates, however, that cirrhosis may follow extensive primary destructive lesions, a view not yet fully accepted, and supports the contention of Kretz that cirrhosis is essentially a reparative process.

Explanation of Plate III.

Fig. 1—The primary lesion. Extensive hyaline necrosis sparing only the tissues about the larger portal spaces. Thirty-eight hours. Dose, 1:1000. Methylene blue and eosin. No. 2 oc., No. 3 obj., Leitz.

Fig. 2—Experimental cirrhosis. Broad bands of newly formed connective tissue surround the islands of normal liver about the portal spaces. In the stroma may be seen newly-formed bile ducts and numerous giant cells. Thirty-six days. Dose, 1:1000 Methylene blue and eosin. No. 3 oc., No. 3 obj., Leitz.

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To Illustrate Dr. Pearce's Article on "Experimental Cirrhosis of the Liver"

Albany Medical Annals, February, 1900

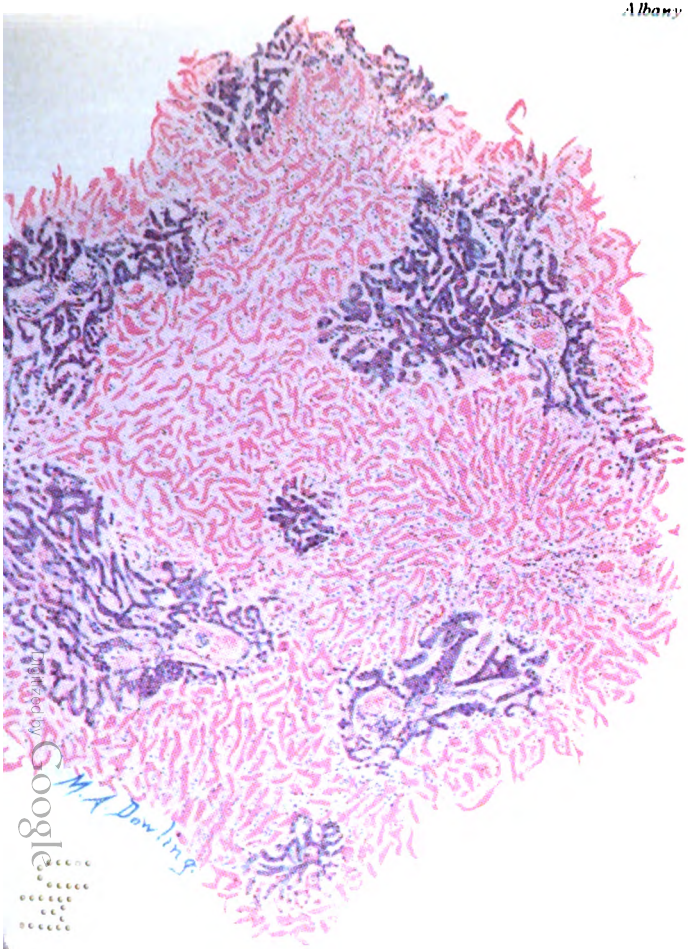

FIG. 1

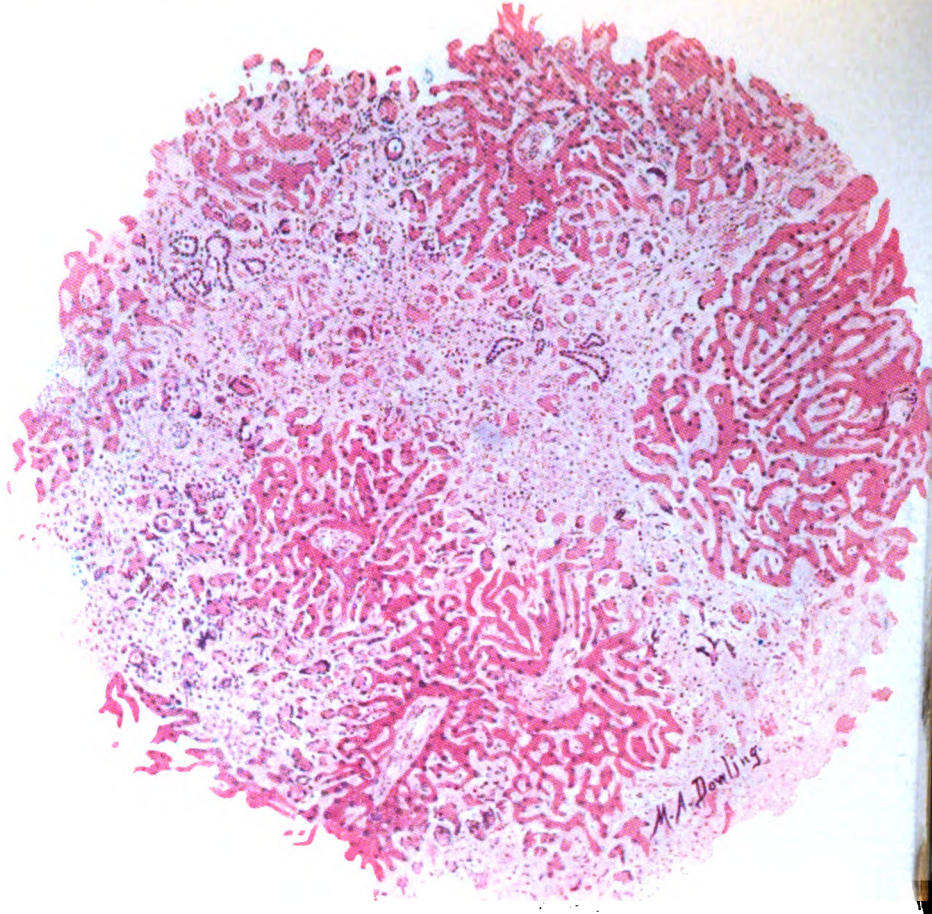

FIG. 2

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EXPERIMENTAL ARTERIOSCLEROSIS.[1]

BY RICHARD M. PEARCE, M. D., AND E. MACD. STANTON, M. D.

(From the Bender Laboratory, Albany, N. Y.)

(Plates I and II)

The complexity of the pathologic picture in the arteriosclerosis of man and the difficulty of determining the nature and sequence of the early changes have led many investigators to attempt the experimental production of the disease in the hope of thus solving some of its many confusing problems. Until within the last two years all such efforts have been unsuccessful. It is true that Thoma described a diffuse arteriosclerosis in the dog as the result of a chronic experimental aortic insufficiency and that Gilbert and Lion[1] produced scattered sclerotic and calcareous changes in the vessels of animals by injecting bacteria and their toxins. Thickening of the vascular walls has been described also as the result of poisoning animals with lead. These results, however, have been inconstant and lack confirmation. Jores,[2] in his excellent monograph on arteriosclerosis published in 1903, reached the conclusion, based on a critical review of the literature, that all experimental methods fail to cause lesions similar to those occurring in man. Various endarterial lesions, obliterative or otherwise, as well as diffuse inflammation and atrophy, have been produced by injections of bacteria or their toxins by the application of irritating substances to the perivascular tissues and by ligation and other forms of mechanical injury; but none of these lesions is analogous to true arteriosclerosis.

[1]This investigation was conducted under a grant from the Rockefeller Institute for Medical Research. Read before the Association of American Physicians, at Washington, May 17, 1905. Published also in *Journal of Experimental Medicine*, 1906, viii, 74.

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It is a curious coincidence that in the same year in which Jores reached this conclusion Josué[3] described experimental lesions in the aorta of rabbits, somewhat similar to those of human arteriosclerosis. These were caused by frequent intravenous injections of adrenalin. With the exception of a few inconclusive experiments of Jores, who gave dogs adrenal tablets in their food in the hope of obtaining lesions due to heightened blood pressure, Josué appears to be the first investigator to attempt the experimental production of arteriosclerosis by the use of the principle of the adrenal gland. His results have been confirmed by Erb,[4] Rzentkowski,[5] Fisher,[6] and others. Their reports include but a small group of experiments, and deal for the most part with the late changes, which they describe variously as arteriosclerosis, atheroma, and calcification. The principal histologic changes to which they call attention are alteration in the elastica and the infiltration of lime salts.

The importance of a method capable of producing an experimental lesion so closely resembling human arteriosclerosis is apparent. It allows an opportunity to study many of the obscure problems of the disease, as the nature of the primary changes, the sequence of these changes, and the combinations which constitute the fully-developed lesion. It was with the hope of elucidating some of these problems that the present investigation was undertaken. The results have been satisfactory beyond all expectation. Vascular changes, capable of throwing much light upon the pathology of arteriosclerosis, and also that of aneurysm formation, have been readily produced. Only a general outline of these will be given at this time, for many of the details of the histologic changes, especially of the process of repair, are so important that they require a more extended study. A consideration of these details is therefore reserved for a future publication, based on a second series of experiments now in progress.

Methods. Rabbits have received in the veins of the ear repeated injections of a 1:1000 solution of adrenalin. The solution was prepared by a chemist, with due regard to asepsis and chemical purity. Physiologic salt solution was used as a medium. In addition to adrenalin (Parke, Davis & Co.) it contained chloretone in the proportion of one-half of one per cent. and a sufficient amount of hydrochloric acid to make the solution faintly acid.

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An initial dose of three minims[1] and the repetition of the same amount every other day has been the usual procedure, though in some experiments the dose has been gradually increased. Not infrequently the early injections cause death from acute dilatation of the heart and pulmonary edema. Such accidents usually occur after any one of the first seven or eight injections. If the animal survives this period it appears to gain a certain amount of immunity, or, at least, tolerance to adrenalin, so that the dose may be gradually increased during several weeks, until twenty to twenty-five minims may be given every day. This increased resistance to adrenalin has been noted also by Erb and Fisher. The animals have been killed after periods varying from a few days to eight and a half weeks.

For histologic study tissues have been preserved in Zenker's fluid, alcohol and six per cent. formalin; imbedded in celloidin; and stained with hematoxylin and eosin, and by Weigert's elastica and Mallory's connective-tissue methods. The scharlach R. and Osmic acid methods have been employed for the demonstration of fat. Sections hardened in Flemming's solution and stained by hematoxylin have been found to be most satisfactory for purposes of general study. By this method the nuclei and areas of calcification stain blue; fat, if present, black. The elastic fibres stand out prominently as light, greenish-yellow, glistening lines, while all other structures are of a faint gray color.

Results. Of twenty animals receiving adrenalin nine succumbed to the acute effects of the drug within fifteen days. These nine represent animals receiving one, three, four, five, seven, and eight injections of adrenalin on alternate days. In some instances death resulted within a few minutes after the injection, in others, after a few hours. The immediate effect of the intravenous administration of adrenalin is collapse with difficult and rapid respiration. The animal lies on its abdomen, with legs outstretched, and head resting on the table or raised in spasmodic respiratory effort. Death, preceded by severe convulsive movements, may occur immediately. Other animals recover from the immediate manifestations only to succumb after a few hours. Upon postmortem examination the usual picture is acute dilatation of the heart and edema of the lungs, with, not infrequently,

[1] Throughout this report the dose will be given in minims. It would be better, perhaps, to use the values of the metric system, but as Josué and others give the dose in minims or drops, we have for purposes of control used the same system of measurement.

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small hemorrhages beneath the pleura and pericardium. In one animal hemorrhages were also found in the adrenal. These acute lesions indicate a very serious disturbance in the terminal vascular territories, and are worthy, perhaps, of further investigation; but as our problem has to do only with the histologic changes in the larger vessels, its scope has been limited to that extent. The theoretic conclusions to be drawn from experimental adrenalin edema and their possible application to acute edema of the lung in man have recently been discussed by Josué.[7]

In but two of this group of nine animals were changes in the vessels demonstrable. These will be discussed later.

The second group of eleven animals represents those receiving from eight to twenty-eight injections during periods varying from sixteen to fifty-nine days. One of these died on the twenty-fifth day from spinal hemorrhage; another on the forty-sixth day, from unknown cause, three weeks after the cessation of injections; the remaining ten were chloroformed. The aorta in six of these showed marked gross lesions; in the other five it was negative, both macroscopically and microscopically. It is of interest that these five animals were all from the same litter, and each weighed about 750 grams at the time of the first injection. Pic and Bonnamour[8] have come to the conclusion that it is impossible to produce vascular lesions by adrenalin in rabbits weighing less than 2000 grams, and quote in support of this opinion their negative experiments with animals weighing about 1200 grams. That this is not an absolute rule is shown by the fact that the most characteristic and advanced lesions in our series occurred in an animal weighing 870 grams at the beginning and 1020 at the end of the experiment. Otherwise, however, our experience with small animals supports the contention of Pic and Bonnamour.

Attempts to produce lesions in dogs have been unsuccessful. Both old and young dogs have been used. One of the latter, a puppy 2120 grams in weight, received in the ear vein in one month one hundred thirty minims of adrenalin in doses rising gradually from four to twenty minims. Although respiratory and cardiac disturbances frequently occurred immediately after injection, thus indicating a definite physiologic action of the adrenalin, no evidence of vascular lesions could be found at autopsy or upon microscopic examination.

Gross Lesions. These appear to be limited to the aorta. The

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involvement of other arteries, as the brachial, carotid, and renal, which Erb describes, we have not found. These lesions in the aorta are most marked in the thoracic portion, and are seldom found below the cœliac axis or in the first portion of the arch. The earliest change in the vessel wall manifest to the naked eye is a faint longitudinal or irregular grayish streak of the intima without thickening. This appearance was seen as early as the ninth day in a rabbit which had received five injections. After eight to fifteen injections, especially if the animal is allowed to live for a week or longer after the last injection, very definite lesions are apparent. These consist of irregular, isolated, or confluent areas, usually slightly depressed, of a pearly gray color and almost constantly calcified. The following protocol illustrates this condition:

Rabbit No. 11. Weight, 2,300 grams. Killed May 2d after injection as follows: March 29th and 31st, 4 minims; April 2d and 4th, 5 minims; April 6th and 8th, 7 minims; April 10th, 10 minims; April 12th, 12 minims; April 14th, 15th and 16th, 15 minims. *Autopsy:* The aorta is distinctly dilated, measuring twelve millimeters in circumference at the arch. Beginning at the origin of the left carotid artery is an irregular patch thirty-seven millimeters long, averaging two and a half millimeters in width, and extending in a spiral course along the aorta for a distance of thirty millimeters so as to completely encircle it. Along this patch the wall of the aorta is slightly dilated. The media is firm, parchment-like and so distinctly calcified that the vessel cracks in several places when the arch of the aorta is straightened. At one side of this large patch are two very small oval areas of similar structure. There is no atheroma or ulceration. All the other organs are entirely negative.

The late lesions occurring after from twenty to twenty-five injections are very well marked. The aorta is more or less distorted, rigid and non-elastic. Irregular dilations alternate with elevated brittle areas of calcification. Distinct ulceration with atheroma is not readily demonstrable. Diffuse calcification is not infrequent and small aneurysmal dilations may be present. The following protocol illustrates the advanced lesions occurring in animals receiving large doses during a considerable period of time.

Rabbit No. 3. Weight, 870 grams. Received first injection of 3 minims in ear vein on November 30, 1904. Similar injections were repeated on alternate days until December 30th, after which date the dose was rapidly increased until it reached 20 minims daily. The animal was killed on January 20, 1905. *Autopsy:* Weight, 1,150 grams. The thoracic aorta

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measures six millimeters in diameter, is distinctly dilated, irregular in outline, stiff and brittle, although the wall is apparently thinned. This condition extends as far as the cœlic axis, beyond which point the abdominal aorta is apparently normal. On opening the aorta the inner surface of the abdominal aorta above the cœlic axis shows numerous yellowish, slightly raised, calcified patches one to one and five-tenths millimeters in diameter, which in the upper portion of the thoracic aorta become confluent. Except in one of the small patches situated in the upper portion of the abdominal aorta there is no evidence of ulceration. All other organs are negative.

The following description from the protocol of a parallel experiment illustrates the tendency to the formation of small aneurysms:

Rabbit No. 2. The aorta averages three millimeters in diameter except at three places where distinct dilations occur. The first of these begins three centimeters below the origin of the aorta and involves the right anterior wall of the aorta for a distance of two centimeters, giving the appearance of a fusiform aneurysm; the diameter of the aorta at this point is four millimeters. A second dilation, two and five-tenths centimeters in length, occurs in the distal portion of the thoracic aorta and a third involves the abdominal aorta for a distance of one centimeter immediately below the cœlic axis. On section the inner surface of the aorta shows sharply circumscribed saccular dilations, varying from one to two millimeters in depth, and corresponding to the protrusions described above. The walls of these aneurysms contain firm placques of calcareous material. The intervening aorta shows a number of yellowish-white elevated areas one to three millimeters in diameter. The aorta below the dilation at the cœlic axis is macroscopically negative.

Histology. In the group presented by the nine rabbits which died during the first two weeks, the vessels of but two showed histologic changes. These were animals which had received four and five injections, respectively. The first died on the fifth day and the second on the ninth day. Scattered through the middle coat of the aorta in each of these are small longitudinal or occasionally irregular, finely granular foci of degeneration. In these areas no nuclei are visible, and the muscle fibres are transformed into a finely granular, almost hyaline material, which stains deeply with eosin. The exact nature of this change is not readily determined, but as the various methods of demonstrating fatty transformation are negative, and those which differentiate elastic fibres show no change in the staining reaction of the latter, the condition would appear to be a simple necrosis limited to the muscle fibres. The elastic tissue has, however, undergone very

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characteristic morphologic changes, which are found only in the degenerate areas, and are due, presumably, to mechanical influences. In the normal aorta the elastic fibres have a distinctly wavy or curled appearance, and are definitely separated from one another. In the areas described the fibres lose this appearance and become straightened and closely approximated. They are also swollen and occasionally appear to be fused together. Fracture of the fibres is seldom seen at this stage of the process.

A more diffuse lesion of this character was found in an animal killed on the twenty-fourth day after receiving eleven injections. The changes involve the entire circumference of the vessel, sparing to a certain extent, the innermost and outermost portions of the media. In this central zone few or no nuclei can be found, and the altered tissue presents a uniform, finely granular appearance, relieved only by the glistening lines of the elastic fibres. The latter, by selective stain, are seen to be so closely massed together that individual fibres can be distinguished only with great difficulty. On either side of this zone the less degenerated portions of the media show irregular areas, which take the hematoxylin stain in a manner very suggestive of early infiltration with lime salts. There is, however, no distinct calcification and no fracture of elastic fibres.

Lesions of great interest in comparison with the above were observed in two rabbits which had received the same number of injections, but which were allowed to live for ten and eighteen days, respectively, after the last injection. In the aorta of each are found a few areas of granular necrosis, but for the most part these areas have been altered by infiltration with lime salts. From the topography of the areas of calcification and their relation to the necrotic foci it is evident that the deposition of lime salts follows the necrosis. It would appear, therefore, that the primary degenerative lesions are well advanced by the end of the third week, and that, after this, but one or two weeks' time is sufficient for advanced calcification. The latter may, however, occur much earlier, for in one rabbit, killed on the sixteenth day, small but very definite foci of lime infiltration were present.

In the areas of lighter deposition of lime it is seen that these salts are first deposited between the elastic fibres, an observation which indicates that the destruction of the muscle fibre is the older, and therefore in all probability the primary lesion. In the areas of advanced calcification, although the elastic fibres appear

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to be completely destroyed by the calcareous transformation, Weigert's stain shows them to be still present, though they stain poorly and are frequently fractured. Not uncommonly at a point of fracture one bundle of fibres overlaps another, the ends being splinted together by an encapsulating mass of lime salts. These fibres are always perfectly straight, except at angles formed by fracture. A definite relation appears to exist between calcification and fracture of the elastic fibres. In areas of the most extensive calcification few breaks in the elastic fibres have been observed, while, on the other hand, they are constantly present in the aneurysmal dilations which show comparatively little calcification.

Lesions of this stage show the first evidence of repair. This is indicated by the collection of newly formed cells about the foci of calcification. These cells are closely massed, surrounded by but a slight ring of protoplasm, and appear to be of connective-tissue origin, though it has been impossible to always distinguish between such and the nuclei of smooth muscle fibres. No accumulation of polymorphonuclear leukocytes, or lymphoid cells, has been seen. Of greater interest are the proliferative changes in the intima. These occur only opposite distinct breaks of considerable depressions in the media, and include proliferation of the lining endothelium and, to a greater extent, the subendothelial tissues. The endothelial cells proliferate to form two or three layers of cells longitudinally arranged, while the subendothelial space, barely visible in the normal aorta, becomes very prominent owing to the presence of closely packed oval nuclei arranged vertically to the lining endothelium. Between the nuclei are delicate, newly formed connective tissue and elastic fibrils. In the late stages the newly formed elastic fibrils are very prominent. In the angle of fracture the nuclei of the media assume a perpendicular arrangement, very striking in contrast to their longitudinal arrangement elsewhere. The entire picture is distinctly that of a compensatory proliferation—an effort to strengthen the weakened point in the vessel wall.

Such are the essential phases of this lesion in the order of their sequence. The more prolonged experiments offer no fundamentally new features, but the combinations of these primary changes in the course of the more extensive involvement of the vessel wall, lead to a complex histologic picture closely resembling advanced human arteriosclerosis. This is seen only in animals

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which have received gradually increasing doses during a period of seven or eight weeks. The vessel wall becomes greatly thickened, not only by infiltration of lime salts, but also by an extensive repair process, which involves the intima as well as the media. Small foci of complete necrosis, analogous to atheroma and entirely different from the primary degeneration, are also seen in areas in which the elastic fibres are completely destroyed. These present a uniform, finely granular appearance, and stain deeply with eosin. The osmic acid method for fat is negative, but a few fine droplets are evident after treatment with scharlach R. About such areas repair takes place, but it is not as active as it is about the masses of lime salts.

The most striking feature of the late histologic picture is the extent of repair in the intima. The latter, with its newly formed connective tissue and elastic fibrils, becomes so greatly thickened that it constitutes in some places a quarter to a third of the entire vessel wall, and offers convincing evidence of the compensatory nature of the repair process.

It is in these late lesions that the small aneurysms are seen. They occur at points where the elastica is so completely destroyed as to be transformed into an indistinct mass of fractured granular and fused fibres. The transition from normal to necrotic fibres is always sharp and distinct, and marked by complete fracture of all elastic tissue. It is worthy of note that in the thinned wall of these aneurysms the degree of calcification is, as a rule, less marked than eleswhere. The adentitia is compressed, but otherwise unaffected.

The changes in other organs include enlargement of the heart, edema, and congestion of the lungs, and occasionally degenerative changes in the heart and skeletal muscles. In one case degenerative lesions were found in a nerve ganglion adherent to the aorta. It was thought that these changes might have some etiologic relation to the vascular lesion, but a thorough study of all our material failed to reveal lesions in other animals or in other ganglion of the same animal. The affected ganglion was in the adventitial tissue of an aneurysmal dilation, and the effects of pressure and disturbed blood supply were sufficient, apparently, to account for the changes observed.

The Mode of Action of Adrenalin. The manner in which adrenalin produces these lesions is a matter of widely varying opinion, and, unfortunately, one which cannot readily be deter-

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mined by our method of experimentation. Until we know more about the toxic action of adrenalin and can distinguish between the lesions due to this action and those due to increased blood pressure, and especially between its direct and secondary effect on the blood-vessels, we can hope for no elucidation of this problem. Drummond,[9] who has recently made a thorough study of the histologic lesions caused by adrenalin, divides all into those due to toxic action and those due to increased blood pressure. It is obvious that such a classification is difficult, for it is impossible to determine to what extent degenerative lesions are due to interference with the circulation through action on the blood vessels.

A discussion of the variety of ways in which adrenalin might act, directly or indirectly, to cause degenerative changes in the media of the aorta would, in the present state of our knowledge, be of little value. The difficulty of reaching definite conclusions is illustrated by the diversity of opinion expressed by those who have previously produced the lesions here described. Josué believes them to be due to a combination of a specific toxic influence and the increased blood pressure. Rzentkowski believes in the latter influence only. Erb ascribes an important influence to disturbance of the vasa vasorum. Fisher thinks that, aside from the increased blood pressure, disturbances of metabolism play an important part. Lissauer[10] believes that the toxic influence is the most important factor, but offers no explanation of its mode of action.

No definite conclusion can be drawn from our own experiments. The observation that the earliest changes occur in the media and are apparently primary in the smooth muscle fibres suggests, in view of the well-known physiologic action of adrenalin on this tissue, a direct and selective toxic action; but the absence of similar lesions in vessels other than the aorta does not support this view. For the same reason, and also because of the absence of changes in the adventitia, the vasa vasorum theory appears to be untenable. On the other hand, if we assume, as is very probable, that the changes in form and arrangement of the elastic fibres are due to the same factor or factors which causes the destruction of the muscle cells, and are not secondary to the latter, we have a strong argument in favor of the influence of a greatly-heightened blood pressure at the time of the ischaemia due to the primary action of the adrenalin. In other words it is possible that at the period of vascular spasm produced by the

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adrenalin the nutrition of the vessel wall is altered. This would not explain the limitation of the lesion to the aorta but the added mechanical disturbance due to the extreme distention of the vessel wall would appear to be sufficient to bring about a condition analogous to anaemic necrosis. These problems, however, must be settled by other methods of experimentation. Although it is impossible to determine to what extent the primary changes are mechanical and to what extent toxic in nature, it is certain that some of the secondary changes, as the fracture of elastic fibres and the formation of aneurysms, are largely due to mechanical factors.

Comparison of the Experimental Lesions and those Occurring in Man. If due allowance is made for the difference in size between the aorta of the rabbit and that of man it must be admitted that the lesions produced in the former as the result of the administration of adrenalin are somewhat similar to those occurring in human arteriosclerosis. They are not, however, analogous. All the essential processes are represented, and, considering the delicate character of the wall of the rabbit's aorta, the lesions are relatively as extensive and cause the same degree of deformity. There is, however, as compared with the human lesion, a difference in the initial lesion and in the degree of atheroma which is insignificant, and limited to the media. Extensive atheroma, however, cannot be expected in a vessel wall as thin as the rabbit's aorta; and, moreover, in none of these experiments has a period of time sufficient for the occurrence of degeneration in areas of excessive intimal proliferation elapsed. More prolonged experiments will yield, it is to be hoped, lesions more conclusive in this respect. For the present the condition may perhaps be regarded as arteriosclerosis for the rabbit, but not as a condition analogous to the arteriosclerosis of man.

In the light of the information gained from the study of these experimental lesions it would be desirable, perhaps, to critically discuss the various theories concerning the nature of arteriosclerosis, and especially the character and sequence of the histologic changes. Such discussion, however, does not come within the scope of this communication, and many minor points must be determined before comparisons are justifiable. It is sufficient for the present to point out the strong support afforded Thoma's view that the primary lesion of arteriosclerosis occurs in the media, and is, essentially, the result of injury to the elastica

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and that the changes in the intima constitute a repair process, the object of which is to compensate for the weakened media and the widened lumen.

Explanation of Plates I and II.

Fig. 1. Gross appearance of a portion of the aorta from an animal which had received 27 injections and was killed on the 29th day. The drawing is twice the actual size of the original specimen.

Fig. 2. Diffuse degeneration of central zone of media; 11 injections; 24th day; haematoxylin and eosin; 4 oc., 3 obj.—Leits.

Fig. 3. Microscopic picture of lesion shown in fig. 1. Destruction of media with infiltration of lime salts; extensive proliferation of intima and subintimal tissue; haematoxylin and eosin; 4 oc., 3 obj.—Leits.

Fig. 4. Elastic tissue stain of an area very similar to the above illustrating extreme destruction of the elastica.

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To illustrate Drs. Pearce and Stanton's article on "Experimental Arteriosclerosis"

Albany Medical Annals. February, 1906

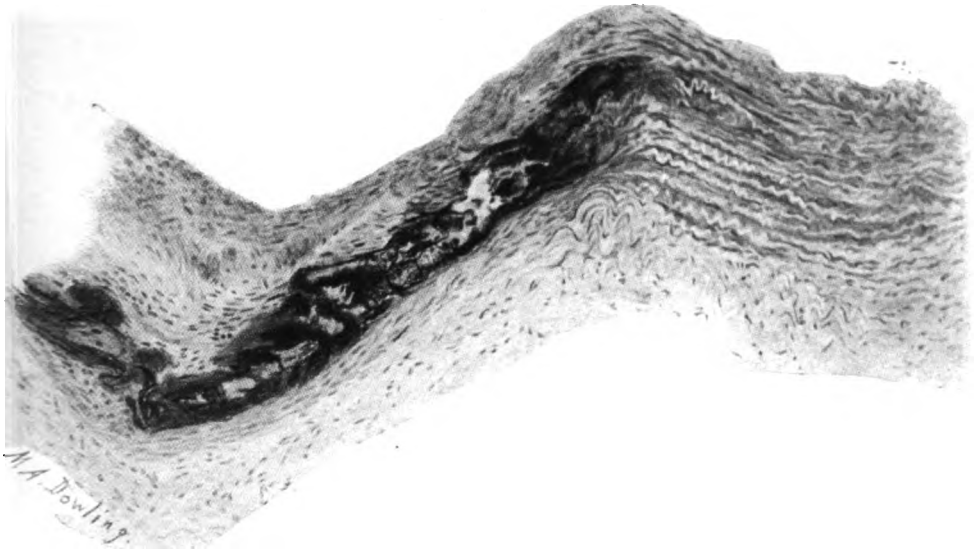

FIG. 3

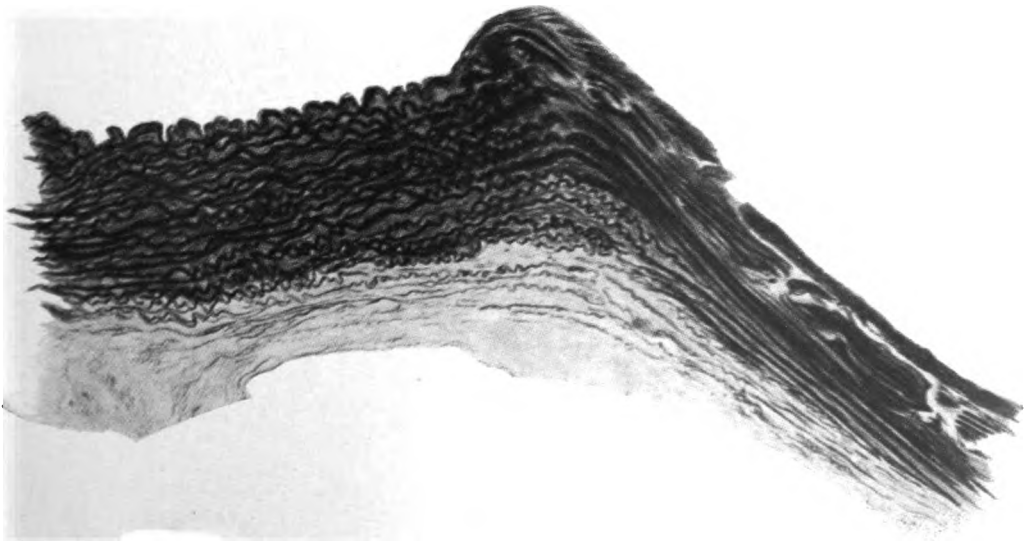

FIG. 4

PLATE II

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Reprinted from ALBANY MEDICAL ANNALS, December, 1905.

THE SEQUENCE OF THE PATHOLOGIC CHANGES IN APPENDICITIS.*

A STUDY OF THE SIGNIFICANCE OF THE LESIONS FOUND IN DIFFERENT STAGES OF APPENDICITIS, BASED ON THE PATHOLOGIC FINDINGS IN A SERIES OF OPERATIVE CASES

BY E. MACD. STANTON, M. D.

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Within recent years much has been written concerning the pathology of appendicitis. The anatomic characteristics of the different varieties of appendicitis, together with the secondary lesions accompanying the primary appendiceal inflammation, have been most carefully described and abundant statistics dealing with the relative frequency of the different types of appendiceal and periappendiceal lesions exist. In spite of all this accumulated knowledge, the subject of the pathology of appendicitis is not by any means a closed chapter, but continues to be prominent in medical discussions and literature. The reason for this, perhaps, may lie in the fact that it has not yet been generally recognized that the different pathologic conditions, as they are encountered at operation in cases of appendicitis, represent, for the most part, simply different stages of an inflammatory process involving primarily the appendix and accompanied, in a large proportion of cases, by a more or less extensive secondary involvement of the peritoneal cavity. Most of the studies dealing with the description and classification of the different pathologic varieties of appendicitis are based on a study of the lesions without reference to the duration of the symptoms previous to the observation

* Published also in Journ. of the Am. Med. Association, 1905, xliv, 1849.

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of the pathologic condition and for this reason such studies throw little light on the pathologic history of the disease.

A study of the pathologic history of appendicitis resolves itself into a study of the processes of inflammation and repair as they occur in this disease, and a knowledge concerning the progress of these processes can best be obtained by a combined clinical and pathologic study of a sufficiently large series of cases, tabulating the pathologic findings according to the time which has elapsed between the onset of the attack and the observation of the pathologic condition. When the lesions are studied in this way, there is found to exist a striking general uniformity of the microscopic appearances at each of the succeeding periods following the onset of symptoms. This uniformity in the microscopic appearances exists in spite of decided variations in the gross appearances of the appendices, and the fact that the microscopic features prominent at one period may be either increased or diminished in preceding or in subsequent stages, shows that we have to do with a continuous process and that it is probable that the majority of cases presenting the characteristic lesions of patients operated on on the tenth day would, seven days earlier, have presented the lesions characteristic of the third day. The results of such studies, therefore, should serve not only as a basis for a knowledge of the pathologic history of the disease, but should aid also in the diagnosis of the probable lesions existing at any given period during the attack.

OBSERVATIONS OF CASES.

The following observations are based on a study of the condition of the peritoneum as found at operation in 485 cases of appendicitis[1] occurring at the Albany Hospital during the past six years, and of the condition of the appendix in 188 of these cases, the descriptions and sections of which are on file in the Bender Laboratory. The pathologic findings in this series of cases were studied with special reference to the relations exist-

1. The data referring to the condition of the peritoneum is taken from the notes made at the time of operation: all else is based on the descriptions and sections on file in the Bender Laboratory. The histologic observations have necessarily been confined to those cases, the sections of which have been preserved and are available for present study. While the anatomic variations, especially as regards the condition of the peritoneum, are so variable as to require a large series of cases on which to base satisfactory observations, this is not the case with the histologic changes which are so uniform that it is not deemed necessary to include a larger series of cases.

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ing between the character of the lesions and the stage of the disease.

In summarizing the results of the observations in this series of cases, those cases operated on during the first, second, third, fourth, fifth and sixth days of the attack are considered in separate groups for each day. Those cases operated on from the seventh to the tenth, from the eleventh to the fifteenth and from the sixteenth to the thirtieth day are considered in three corresponding groups; while all cases operated on one month or more after the occurrence of a definite attack are considered as a separate group.

The following is a summary of the more striking features of the pathologic process:[2]

First Day Group.—This was made up of ten patients operated on during the first twenty-four hours following the onset of symptoms. In two cases (20 per cent.) there was a sero-purulent intraperitoneal exudate without perforation of the appendix. In one other case, the omentum was adherent by a fibrinous exudate to a gangrenous appendix. The gross appearances of the nine appendices studied histologically varied greatly. Two showed plainly visible gangrenous areas, one was described as normal, while in others the only macroscopic evidence of disease was a congestion or slight opacity of the peritoneum, with a swollen or hemorrhagic mucosa.

In sharp contrast to the often apparently insignificant gross lesions is the microscopic picture, which is essentially similar in all cases and consists of an intense, diffuse, polynuclear leucocytic infiltration with focal areas of hemorrhage and necrosis involving all coats with a more or less extensive destruction of the mucosa and, in many cases, a fibrinous or fibrino-hemorrhagic exudate on the peritoneal surface. One of the most striking features in these cases is the presence throughout the majority of the sections of numerous areas of necrosis. These areas are larger, but are not more numerous in those cases which show macroscopic evidences of gangrene.

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2. The accompanying charts show graphically the relative frequency of the various types of lesions grouped according to the different periods as enumerated above and also serve to give an idea of the relationships existing between the character of the pathologic lesions and the duration of the disease. The absence of irregular fluctuations in the platted curves is evidence that the series of cases here studied has been sufficiently large for the purposes of this investigation, although the relative heights of the different curves must vary somewhat in different series of cases.

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Second Day Group.—This was made up of twenty-three patients operated on during the second twenty-four hours following the onset of symptoms. In eight (34.8 per cent.) of the cases of this group intraperitoneal fluid exudates, usually of considerable extent and of a sero-purulent or purulent character were present. As in the first-day cases, the appendices in this group which were studied histologically, presented no uniformity as to gross appearances. Some of them are described as "gangrenous," others as "catarrhal" and "ulcerative" or "slight periappendicitis."

Microscopically, all the appendices show an intense leucocytic infiltration involving all coats, together with a more or less extensive ulceration of the mucosa, while 70 per cent. show a well-marked fibrinous or fibrino-purulent exudate on the peritoneal surface. In those cases which presented macroscopic evidence of gangrene the areas of necrosis as seen microscopically are decidedly more extensive than in the similar cases of the first-day group, while in those cases which did not present macroscopic evidences of gangrene the focal areas of necrosis so prominent in the first-day cases are still evident in the majority of sections, but are often obscured by the leucocytic infiltration.

Third Day Group.—This was made up of fifty-three patients operated on during the third day following the onset of symptoms. Twenty-nine (53.7 per cent.) of the cases in this group were characterized by intraperitoneal fluid exudates which were of a distinctly purulent character and usually described as periappendiceal abscesses. The macroscopic evidences of disease were distinctly more prominent than in the earlier cases. Forty per cent. of the appendices studied histologically were described as "gangrenous" and all but three of the others as "acute" or "acute ulcerative."

Microscopically, two recurrent cases show decided chronic changes, but no evidence of an acute process. The remaining cases all show a diffuse inflammation like that seen in the earlier groups. In the macroscopically gangrenous cases the necrosis is prominent, while in the non-gangrenous cases focal areas of necrosis are seen only in the mucosa. The most striking histologic feature which distinguishes this group from the earlier groups is the evidence of beginning repair as seen by the presence of fibroblasts in all sections. These new-formed connective tissue cells are especially numerous in the region of the peri-

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toneum, although present in other areas, particularly in those cases showing the least marked leucocytic infiltration.

Fourth Day Group.—This was made up of thirty-one patients operated on during the fourth day following the onset of symptoms. In seventeen (54.5 per cent.) of the cases in this group purulent periappendiceal exudates usually described as abscesses were present. With the exception of one normal and one chronic atrophic appendix (microscopic diagnosis), all of the appendices in this group presented well-marked anatomic changes in general similar to those seen in the third-day cases.

Microscopically, the gangrenous cases show large areas of complete necrosis, the histologic picture differing but little from that seen in the gangrenous cases of the third-day group. In sections of the non-gangrenous cases, and in sections taken at some distance from the necrotic areas in the gangrenous appendices, the most noticeable histologic feature which distinguishes this group from the preceding one is a decided increase in the relative number of fibroblasts and the presence of numerous lymphocytes and, in several cases, plasma cells. In those cases accompanied by a periappendiceal exudate a few fibroblasts and many new-formed blood vessels can be seen extending into the exudate from the peritoneal surface. Focal areas of hemorrhage into the exudate occurring from these new-formed blood vessels are seen in many of the sections.

Fifth Day Group.—This was made up of twenty-seven patients operated on during the fifth day following the onset of symptoms. In fifteen (55.5 per cent.) of the cases of this group periappendiceal suppuration was noted. With the exception of one recurrent case, all of the appendices presented easily recognizable anatomic changes most evident in the mucosa or on the peritoneal surface.

Microscopically, the lesions may be divided into two rather sharply defined groups. In the cases presenting macroscopic evidence of gangrene, the necrosis and polynuclear leucocytic infiltration is the predominating characteristic, although the repair process is well advanced in several instances. In the non-gangrenous cases the polynuclear leucocytes have practically disappeared except at the surfaces of the ulcerations in the mucosa and of the periappendiceal exudates. Throughout the coats of the appendix there is a marked increase in the number of fibroblasts and often an intense lymphocytic infiltration. In the periappendiceal exu-

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dates the new-formed blood vessels penetrate to a greater distance than in the fourth-day group and this granulation tissue is decidedly richer in fibroblasts.

Sixth Day Group.—This was made up of twenty-four patients operated on during the sixth day following the onset of symptoms. Twelve (50 per cent.) of the cases in this group showed evidence of periappendiceal suppuration and all the appendices showed well-marked anatomic changes. The partially organized periappendiceal exudates were very noticeable in those cases accompanied by abscess formation.

Histologically, the repair processes are decidedly more advanced than in the fifth-day group. The gangrenous cases show well-marked evidences of repair, the histologic picture of which is similar to that seen in the non-gangrenous cases of the preceding group. A number of these cases, however, present the picture of a fresh acute process engrafted on the subacute process, there being a diffuse leucocytic infiltration with areas of hemorrhage and necrosis, the latter often involving areas rich in fibroblasts. The non-gangrenous cases now show areas in which the fibroblasts are massed together and elongated so as to resemble young connective tissue cells. Small ulcers in the mucosa have apparently been largely repaired.

Seventh to Tenth Day Group.—This was made up of one hundred and six patients operated on from the seventh to the tenth day of the attack. Fifty (47.1 per cent.) of the patients operated on during this period had also periappendiceal suppuration, which in all but six cases was more or less localized and usually accompanied by marked evidences of organization. Anatomic changes, for the most part, were well marked, particularly so in those cases characterized by partially organized periappendiceal exudates. In the cases unaccompanied by periappendiceal exudates the anatomic lesions were decidedly less prominent than in the earlier groups, and four of the appendices studied histologically were described anatomically as cases of catarrhal appendicitis.

Histologically, the repair process has become still more advanced, so that in 18 per cent. of the appendices in this group the organization is so far advanced as to present the picture of a distinctly chronic process, the evidence of a previous active inflammation being shown by the presence of new-formed fibrous tissue which is rich in connective tissue cells. In addition to

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the new-formed connective tissue in these cases, numerous focal collections of lymphocytes are seen, which are most noticeable in the subperitoneal tissues and muscular coats. In 64 per cent. of the appendices in this group the presence of the fibroblasts and other evidences of active repair is noticeable, being most marked in those cases showing partially organized periappendiceal abscesses. Eighteen per cent. of the cases show evidences of an acute process, which is seen as a diffuse polynuclear leucocytic infiltration, often accompanied by hemorrhage and necrosis. In all but one of these acute cases, however, there are also evidences of an older subacute process.

Eleventh to Fifteenth Day Group.—This was made up of forty-eight patients operated on from the eleventh to the fifteenth day following the onset of symptoms. In this group in but sixteen cases (33.3 per cent.) were periappendiceal abscesses found, and when present the pus usually occurred in small collections surrounded by thick masses of new-formed connective tissue. The macroscopic appearances of the appendices in this group varied greatly: Two were described as "gangrenous," two as "acute," three as "normal," and the rest as "subacute," "chronic," "chronic obliterative," "chronic periappendicitis" and "catarrhal." Except in those cases showing an acute process and in those accompanied by evidences of periappendiceal organization, the gross changes in the appendices, as a rule, were not prominent.

Microscopically, 68 per cent. of the appendices present lesions of a typically chronic character, the most constant feature of which is an increase of connective tissue, usually well marked and accompanied by conspicuous focal collections of lymphocytes; the latter occur, as a rule, within the perivascular and interstitial lymph channels of the peritoneal and muscular coats. An additional 10 per cent. show a less advanced stage of repair corresponding to the predominating lesion in the preceding group. Ten per cent. show changes confined to the mucosa, such as are usually described as catarrhal appendicitis. Ten per cent. show the presence of acute inflammation, in addition to subacute or chronic changes.

Sixteenth to Thirtieth Day Group.—This was made up of forty-six patients operated on from the sixteenth to the thirtieth day following the onset of symptoms. Abscesses were present in 19 per cent. of the patients operated on at this period of the dis-

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ease; this decrease in the frequency of pus being accompanied by a corresponding increase in the number of cases showing adhesions without the presence of pus. In the cases in which there was no histologic evidence of an acute or subacute inflammatory process, the macroscopic changes in the appendices were not prominent except in those cases showing an obliteration of the lumen or evidences of periappendiceal organization.

Microscopically, 69 per cent. of the cases show only chronic changes. In these the new-formed connective tissue is more fibrous than in the similar cases of the preceding group, while the focal collections of lymphocytes, so prominent in the

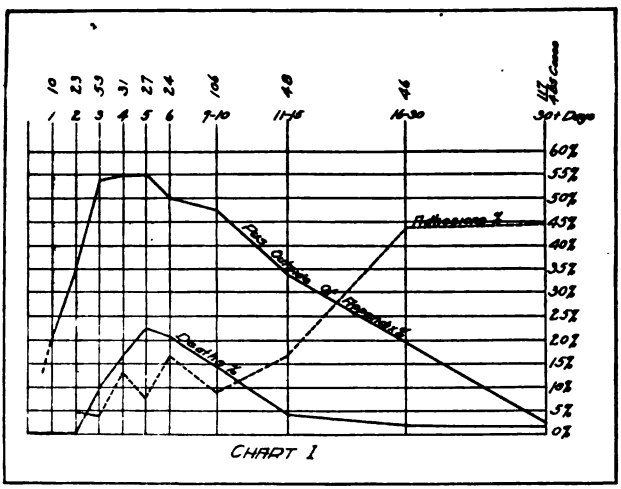

Chart 1.—Condition of the peritoneum and death rate. The term "pus outside of appendix" is used to include all cases accompanied by purulent intraperitoneal fluid exudates, either localised or general. The term "adhesions" is limited to those cases presenting organized adhesions without the presence of pus.

preceding group, are now less numerous. A few cases still show acute or subacute lesions, in addition to more chronic changes. Ten per cent. of the cases must be considered as examples of catarrhal appendicitis, as the demonstrable pathologic changes are confined entirely to the mucosa.

Patients Operated on One Month or More After a Well-defined Attack.—In this group are included one hundred and seventeen patients, having, for the most part, histories of long-standing chronic, recurrent or relapsing appendicitis. In three cases (2.5 per cent.) small foci of pus were found in connection with extensive adhesions. In 44 per cent. of the cases there were

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well-marked adhesions, without the presence of pus. With the exception of the cases of chronic obliterative appendicitis, the macroscopic changes in the appendices were usually not prominent, and many of the cases which show an extensive increase of interstitial connective tissue were described as macroscopically normal.

No appendices in this group show microscopic evidence of an acute or subacute inflammatory process. Six per cent. of the

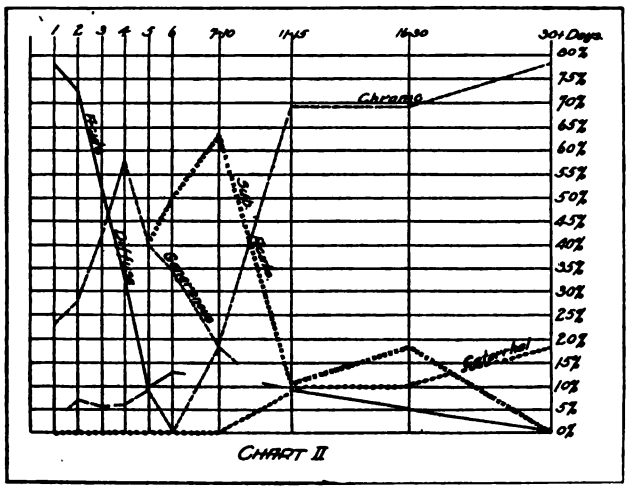

CHART II

Chart 2—Histologic condition of appendix. The term "acute diffuse" is used to include all appendices showing a diffuse polynuclear leucocytic infiltration without the presence of macroscopic evidences of gangrene. Under the term "gangrenous" are included all appendices showing macroscopic areas of gangrene with or without perforation. Under the term "subacute" are included all appendices showing evidences of active repair unaccompanied by a polynuclear leucocytic infiltration. Under the term "chronic" are included all appendices showing a distinct increase of connective tissue without evidences of active repair or leucocytic infiltration. All appendices showing changes confined to the mucosa are included under the term "catarrhal."

appendices are microscopically normal; 16 per cent. are examples of catarrhal appendicitis; 52 per cent. are microscopically examples of more or less well-defined chronic interstitial appendicitis; 26 per cent. are examples of chronic obliterative appendicitis.

SUMMARY.

The character of the histologic changes is essentially similar in all of the appendices of this series which were removed during the first few days of the disease and is that of a severe, diffuse inflammation, accompanied by focal areas of hemorrhage and

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necrosis. These focal areas of necrosis may increase in extent during the first few days and give rise to macroscopic areas of gangrene or they may remain of microscopic size and be quickly repaired. The various anatomic varieties, such as the gangrenous, perforative and ulcerative forms, are determined by the extent and distribution of these necroses.[3]

Evidences of repair are seen as early as the third day, and in the non-gangrenous cases the histologic picture of an acute process has changed to that of a distinctly reparative process by the fifth day. In those cases in which the necrosis is so extensive as to give macroscopic evidences of gangrene, the histologic picture of an acute process persists for a longer period, but even in these cases (unless there is a later acute process engrafted on the earlier lesion) the evidences of repair are by the sixth or seventh day the predominating feature of the lesion. Evidences of a recurrent acute process are by no means uncommon, and were present in from 10 to 15 per cent. of all cases after the first week.

During the second week of the attack the repair proceeds rapidly. Fibroblasts, new-formed blood vessels and lymphocytes making up the chief features of the histologic picture. The rapidity with which the repair of the appendix itself is accomplished depends chiefly on the extent of the primary destruction and on the presence or absence of a periappendiceal exudate. By the end of the second week, in the majority of cases, the repair is so far advanced that the new-formed connective tissue may constitute the only evidence of a previous inflammation, although in cases with extensive periappendiceal exudates evidences of active organization of the exudate itself are still to be seen.

Except for the completion of the repair in those cases accompanied by more extensive periappendiceal lesions, the histologic changes occurring after the second week are seen chiefly in the more fibrous nature of the new-formed connective tissue which persists so as to be readily recognizable in the majority of cases. Of the patients operated on one month or more following an

3. In connection with the well-known difficulties encountered in attempting to predict the subsequent course of a case of appendicitis seen during the first few days of the disease, it is a fact worthy of emphasis that the early histologic changes were essentially similar, irrespective of the severity of the clinical symptoms, in all the cases observed; and that the later more important gross changes, such as gangrene and perforation, were dependent on the apparently more or less accidental factors which determined the extent and distribution of the necrosis.

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acute attack, 78 per cent. were cases of chronic interstitial or chronic obliterative appendicitis very often accompanied by adhesions. Six per cent. of the appendices were apparently normal, while in 16 per cent. the demonstrable pathologic changes were confined to the mucosa.

A notable feature seen in the histologic examination of these cases is the fact that in no instance was the pathologic change confined to the mucosa in the appendices examined during the first ten days of the attack.

In this series of cases, purulent fluid outside of the appendix was present in 51 per cent. of the patients operated on from the third to the tenth day of the attack.[4] After the tenth day the relative number of cases accompanied by abscesses decreases steadily, while on the other hand occurs corresponding rise in the number of cases presenting adhesions without the presence of pus, which would seem to indicate that resolution by absorption had played an important rôle in the repair of this lesion. This is doubtful, however, and is probably in large measure due to the fact that the involvement of the peritoneal cavity was less extensive in those cases in which operation was delayed. In a number of cases, however, the adhesions were so massive as to leave little doubt of the previous presence of an extensive periappendiceal exudate.

After the third day the exudates on the peritoneal surface contain highly vascular granulation tissue, and it is probable that the high operative death rate between the third and tenth days in part may be accounted for by absorption from the denuded granulating surfaces as well as by the extent of the peritonitis and the bad general condition of the patients.

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4. This includes the cases of general peritonitis as well as those accompanied by a more localized periappendiceal exudate. According to the reports of the operations, the cases of general peritonitis were distributed as follows:

First day	No case.
Second day	One case with recovery.
Third day	Seven cases with five deaths.
Fourth day	Four cases with four deaths.
Fifth day	Six cases with five deaths.
Sixth day	Four cases with four deaths.
Seventh to tenth day	Six cases with six deaths.
Eleventh to fourteenth day	One fatal case.

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Reprinted from ALBANY MEDICAL ANNALS, December, 1905.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX, WITH A REPORT OF THREE CASES.

Read before the Medical Society of the County of Albany, November 8, 1905.

BY LEON K. BALDAUF, M. D.

(From The Bender Laboratory, Albany, N. Y.)

The recognition of primary carinoma as a not infrequent disease of the appendix has been brought about during the past ten years as the direct result of the increasing tendency to examine microscopically all tissues removed by the surgeon. Casuistic reports of instances of this disease, thus brought to light, have appeared in rapid succession since 1896. Letulle and Weinberg, Harte and Willson, A. O. J. Kelly, Elting and Moschowitz have each reported small groups of cases observed in comparatively short periods of time. Their communications containing, as they do, general conclusions drawn from a critical review of the literature, have done much to bring the important facts concerning primary carinoma of the appendix to the general attention of the profession. Nevertheless from a perusal of this literature it is evident that many points are still in doubt and that final general conclusions can be reached only after a much larger number of cases have been placed on record.

It is with the desire therefore to add to the material already available, and not necessarily to present anything new, that this communication comprising a report of three cases and a brief summary of those already described is presented.

Case I—Records of the Bender Laboratory, Surg. Path. No. 04:128.

Clinical History—Mr. H., male, aged thirty-eight, was admitted to the Albany Hospital on February 22, 1904: service of Dr. Albert Vander Veer. *Family history*—Negative. *Past history*—Typhoid fever at fourteen; otherwise negative. *Present illness*—On Sunday, February 21st, the patient experienced sharp pains radiating from the center of the abdomen

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to the right iliac fossa; several attacks of vomiting; no constipation. Blood count showed a leucocytosis of 19,000. *Clinical Diagnosis*—Acute appendicitis.

Operation, February 22, 1904—"Appendix bound down by adhesions and underneath umbilicus. Beginning peritonitis. Appendix easily removed." Recovery uneventful. Discharged March 9, 1904.

Pathological Examination—The specimen consists of the distal portion of the appendix, which is five centimeters in length. The meso-appendix is considerably thickened. The peritoneal surface is covered with greyish yellow fibrin. The lumen is patent throughout. The mucosa, which in general, is of an opaque yellowish color, and deeply injected, exhibits a few small foci of necrosis. *Anatomical Diagnosis*—Acute appendicitis.

Microscopic Description—The lumen is much smaller than normal and contains desquamated epithelial cells, leucocytes and granular debris. The mucosa, slightly infiltrated with leucocytes, is intact in about two-thirds of its circumference, but has entirely disappeared at that portion of the organ to which the mesentery is attached. Here is a slightly irregular ulcerated surface. The tissue beneath this ulcer is composed of closely arranged connective tissue forming small alveoli, in which are masses of epithelial cells. This new growth replaces entirely the mucosa at this point and invades the muscular coat. The masses of cells are of small size near the base of the ulcer, but increase in size as the muscularis is reached; though in the outer portions of the latter they again diminish in size and are not very abundant. Beneath the peritoneum are found numerous nests of epithelial cells larger than those seen in any other portion of the appendix. These pass for a short distance into the loose fatty tissue of the meso-appendix, extending apparently along the lymphatics. The cells composing the epithelial masses are oval or polygonal in shape with considerable light protoplasm and vesicular nuclei. No tendency to tubular arrangement is evident. The stroma is a loose connective tissue with numerous lymphoid and plasma cells.

Except at the mesenteric attachment the serosa is obscured by a mass of young granulation tissue diffusely infiltrated with leucocytes and containing small areas of haemorrhage.

Microscopic Diagnosis—Carcinoma simplex of the appendix with ulceration. Acute appendicitis; periappendicular suppuration.

Case II—Records of the Bender Laboratory, Surg. Path. No. 04:200.

Clinical History—Mr. B., aged twenty-three, was admitted to the Albany Hospital on March 15, 1904; service of Dr. W. G. MacDonald. *Family history*—Negative. *Previous history*—Negative. *Present illness*—Patient thinks it began in September, 1903, when he had severe pains in right iliac region lasting for a week. He had a similar but more severe attach in October. Present attack began on evening of March 13th, with pain in right lower quadrant of abdomen. Pain of varying severity has continued since. *Clinical Diagnosis*—Subacute appendicitis.

Operation, March 18th—"Appendix removed with difficulty."

Pathological Examination—Specimen consists of appendix and a piece of blood stained fatty tissue. The appendix considerably thickened meas-

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ures seven centimeters in length and eight-tenths of a centimeter in greatest diameter. The serosa is covered with tags of fairly firm fibrous tissue. The mucosa is swollen and granular, while the lumen is completely obliterated at a point five centimeters from the distal end. The fat tissue accompanying appendix is haemorrhagic and firmer than usual.

Anatomical Diagnosis—Chronic appendicitis and periappendicitis.

Microscopic Description—The lumen of the appendix is entirely obliterated, and mucosa and submucosa are replaced by a new growth of loose connective tissue, in the meshes of which are epithelial cells closely massed. This new growth penetrates to a slight extent the muscular coat, and at cnly one point, opposite the attachment of the meso-appendix, the masses of epithelial cells reach the subserous tissues. Here however the invasion is sharply limited, and no extension to the meso-appendix is apparent. The muscular and subserous coats show evidence of a slight chronic inflammation, but it is impossible to say whether the obliteration of the lumen preceded or was the result of the new growth. Although serial sections have been made at various levels of the tumor, it has been impossible to determine definitely this question. Above the level of the tumor the organ shows evidence of a mild chronic inflammation, but is otherwise negative.

Microscopic Diagnosis—Carcinoma simplex of appendix with obliteration of lumen. Chronic appendicitis.

Case III—Records of the Bender Laboratory, Surg. Path. No. 04:406.

Clinical History—Miss A., aged eight years, admitted to the Albany Hospital on May 14, 1904, service of Dr. Edgar A. Vander Veer. Nothing of interest in family or previous history. There were no symptoms referable to the appendix until May 14th, when a severe acute attack of appendicitis developed. At the operation, on May 16th, the appendix was found to be surrounded by an inflammatory mass, which was adherent also to the omentum. In the manipulations attending the removal of this mass, it ruptured and a small amount of pus escaped.

Pathological Examination—Specimen consists of appendix measuring five and five-tenths centimeters in length, the upper half of which averaging five millimeters in diameter, is practically normal. The lower half is buried in a mass of partially organized tissue which surrounds the tip of the appendix in a layer approximately five millimeters in thickness. The wall of this portion of the appendix is thickened and indurated. The mucosa is injected, and at one point shows a superficial loss of substance. Lumen normal. Accompanying the specimen is a piece of omentum measuring 4 x 3 x 1.5 centimeters, showing a core of soft yellowish material surrounded by a zone of translucent granulation tissue.

Anatomical Diagnosis—Partial organization of periappendicular abscess.

Microscopic Description—The organ is entirely surrounded by a mass of granulation tissue, which in some places is quite fibrous while in other places it is very loose and vascular. Leucocytes are abundant throughout, and here and there are grouped in distinct foci. The meso-appendix is extensively involved. The appendix, greatly distorted, is found a little

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to one side of the center of this mass. The lumen is compressed, triangular in shape, and contains a few leucocytes and a small amount of granulate material. A very definite mucosa is seen, but the glands are few in number and irregularly arranged. The cylindrical surface epithelium of the mucosa is very distinct and show a superficial ulceration over an area corresponding to a new growth which involves the submucosa. Here the mucosa contains but few glands and several small irregular masses of epithelial cells separated by a loose stroma rich in lymphoid and plasma cells. This new growth involves the entire submucosa, in which the masses of epithelial cells are larger and the stroma more fibrous. There is no invasion of the muscular coat.

Microscopic Diagnosis—Carcinoma simplex with ulceration; periappendicular abscess.

With the exception of Case III, which is the first reported instance of cancer of the appendix occurring in the first decade of life, these cases add little that is new to our knowledge of cancer of this organ. They however increase the number of reported cases available for comparison and as the total is now 34, if we include the three here reported, a brief resumé of the subject may be justifiable.

Summary of Reported Cases of Primary Cancer of the Appendix.

In the following paragraphs is given a brief summary of each of the cases* of primary cancer of the appendix reported prevous to 1905. The first twenty are those examined and accepted by Elting in 1903. To these, others since reported have been added and although the list may not be completed, it represents the result of a very thorough search of the literature. No case has been included unless the diagnosis was confirmed by microscopic examination.

1. *Beger* (1882). Male, aged forty-seven. Three and one half years before final operation a tumor of right inguinal region was incised; a litre of pus was removed; sinus persisted. Adenocarcinoma of appendix involving caecum by extension; metastases in retroperitoneal lymph nodes. Died thirty-six hours after operation.

2. *Stimson* (1896). Female, aged forty-four. Severe attack of appendicitis ten years previously. Two mild attacks within two months before operation. "Degenerated carcinoma."

3. *Letulle and Weinburg* (1897). Autopsy on individual dying of tuberculosis. Starting point of carcinoma at line of fusion in appendix, the lumen of which had been obliterated by preexisting chronic inflammation.

*Since preparing this list Kelly and Hurdon have reported three additional cases. See Kelly and Hurdon, The Vermiform Appendix and its Diseases, W. B. Saunders and Co., Philadelphia and London, 1905.

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4. *Letulle and Weinburg* (1897). Terminal extremity of appendix seat of a peculiar adenomatous hyperthrophy associated with obliterative appendicitis. The carcinoma had begun in scar and had involved all the coats of the appendix.

5. *Mosse and Daunic* (1897). Female, aged fifty. Autopsy. No history of appendicitis. Tumor in mucosa and muscularis in part alveolar and in part cylindrical cell in type.

6. *Wright* (1898). Autopsy. No history. Adeno-carcinoma at base of appendix. Peritonitis due to perforation of appendix.

7. *Hurdon* (1900). Female, aged twenty-four. Pain in lower part of abdomen and back since first child birth, associated latterly with constant aching in right lumbar region. Operation for retroflexed uterus; appendix involved in dense adhesions. Adeno-carcinoma involving all coats of appendix.

8. *Giscard* (1900). Male, aged thirty-seven. Two severe attacks of appendicitis within nine months. Operation; abscess about appendix; adeno-carcinoma.

9. *Rolleston* (1900). Female, aged twenty-six. Four attacks of appendicitis within fifteen months. "Spheroidal-cell carcinoma near tip." In poor health several months after operation.

10. *Letulle and Weinburg* (1900). Twelve and a half years of age. "Muco-membraneous colic" since infancy; history of two attacks of appendicitis at intervals of a year. Operation after subsidence of second attack, which was very acute. Appendix adherent to iliac fossa, upper portion dilated, lower portion contracted, contains an enterolith. *Histological examination*—chronic appendicitis with ulceration in upper portion and obliteration and carcinoma in lower portion.

11. *Letulle and Weinburg* (1900). Autopsy. No history. Chronic obliterative appendicitis with cancer at tip of organ.

12. *McBurney* (1901). Female, aged twenty-three. Attack of appendicitis two years before she came under observation. A second attack two months before operation. Strictures at base and tip of appendix; tumor at tip. Carcinoma simplex.

13. *McBurney* (1901). Male, aged thirty. Autopsy. No previous history of appendicitis. Carcinoma simplex.

14. *Goffe* (1901). Female, aged fifteen. For more than a year pain in the appendiceal region on exercising. Chronic appendicitis. Carcinoma simplex.

15. *Harte and Willson* (1902). Female, aged twenty-four. At nineteen appendicitis; in bed four weeks. Free from symptoms for three years. At twenty-three, during period extending over whole winter, experienced pains similar to those three years previous. Symptoms disappeared finally, but reappeared in the summer. Operation—almost complete obliteration of appendix. Scirrhus carcinoma at tip.

16. *Harte and Willson.* Male, aged twenty-five. Eight months prior to the operation had more or less continuous pain in the right iliac fossa. Operation—adhesions; perforation, acute suppurative appendicitis. Carcinoma simplex near tip.

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17. *Wier* (1902). No clinical history or pathological description. "Carcinoma." No return after three years.

18. *Jessup* (1902). Female, aged thirty-six. No symptoms of appendicitis; operation for disease of uterine adnexia. Cyst of ovary. Appendix bound down with adhesions and therefore removed. Adeno-carcinoma in middle third.

19. *Kelly, A. O. J.* (1902). No clinical history. Operation—acute ulcerative appendicitis. Carcinoma simplex.

20. *Kelly, A. O. J.* (1902). Male, aged eighteen. Well until eight days prior to admission, when symptoms of acute appendicitis developed. Operation—pus about appendix, acute ulcerative appendicitis. Carcinoma simplex at base.

21. *Elting* (1903). Male, aged eighty-one. Autopsy. No symptoms of appendicitis. Colloid cancer of appendix with perforation. No metastases.

22. *Elting* (1903). Female, aged thirty-six. Patient enjoyed good health until eight years previously, when she had an attack of what was called "peritonitis," from which she made a fairly good recovery. Operation for "pelvic disease." No symptoms of appendicitis. Appendix removed with pelvic organs. Obliteration of lumen of entire appendix with carcinoma simplex of distal end. In good health three years after.

23. *Elting* (1903). Male, age ten. Present illness began in January, 1902, with an attack of acute appendicitis which was associated with the formation of an indurated mass in the right iliac fossa, in which after a short time an abscess formed, which opened internally in the right lower quadrant of the abdomen. The sinus still existed when patient was admitted to the hospital. Patient had lost forty pounds. Operation—new growth involving appendix, caecum, ilium, and portions of colon and jejunum, with metastases in adjacent lymph nodes. Died about two weeks after operation. "Primary colloid carcinoma of the appendix of an adenomatous type."

24. *Moschcowitz* (1903). Male, aged thirty-seven. Disturbance for three years, supposed to be alcoholic gastritis; later symptoms of appendicitis with general peritonitis. Operation—general peritonitis. Appendix surrounded by adhesions and partially gangrenous with tumor at tip size of a bean. Adeno-carcinoma. No recurrence eighteen months after operation.

25. *Moschcowitz.* Female, aged twenty. Typical attack of appendicitis. Operation—acute inflamed appendix; carcinoma simplex one inch from tip.

26. *Moschcowitz.* Female, aged twenty-four. Five months pregnant. Foetal movements felt for two weeks. Present history five days duration. Pain in epigastrium, fever, leucocytosis. Exploratory laparotomy. Appendix adherent to iliac fossa. Chronic appendicitis; medullary carcinoma of distal portion.

27. *Burnam* (1904). Male, aged twenty-five years. For two years patient had recurring attacks of pain in right lower quadrant of abdomen. Operation—acute appendicitis with adeno-carcinoma of distal end of appendix.

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28. *Norris* (1904). Female, aged twenty-seven. No history of appendicitis. Operation for retroflexed uterus, pyosalpinx and inguinal hernia. Appendix removed because of reddened and adherent distal end. Obliterative appendicitis with carcinoma simplex at tip.

29. *Neri* (1904). Male, aged twenty-nine. Repeated attacks of appendicitis. Chronic appendicitis with adeno-carcinoma.

30. *Jones and Simmons* (1904). Female, aged twenty-six. Four attacks in twelve years, termed colic. Chronic appendicitis with carcinoma simplex at base of appendix.

31. *Cullingworth and Corner* (1904). Female, aged thirty-one. Had had two attacks of pain in right side. Operation for tumor of right broad ligament. Appendix removed on account of bulbous enlargement at distal end. "Spheroidal cell" carcinoma. No recurrence after three years.

Frequency of occurrence. The older statistics, as quoted by A. O. J. Kelly, indicate that before the days of routine microscopic examination carcinoma of the appendix was but rarely seen. Thus in 40,838 autopsies at the Vienna General Hospital from 1870-1892 carcinoma of the appendix occurred, according to the compilation of Madyl and Nothnagel, but twice. Leichtenstern's series of 770 cases of intestinal carcinoma contains three examples of cancer of the appendix. Kelynack in 1893 could find no record of an undoubted primary cancer of the appendix. In this connection he quotes the records of four London hospitals which gave a total of 15,481 new growths but with no mention of a neoplasm of the appendix. Since that time thirty-one cases nearly all detected only upon microscopic examination have been reported. In 1900 Hurdon found but ten cases in the literature and of these but three were confirmed by microscopic examination. Elting in 1903 brought together forty cases, only twenty of which however he accepted as primary. With the three cases here reported the total number of cancers apparently primary in the appendix and confirmed by a microscopic examination is now thirty-four. Cancer of the appendix is therefore no longer a rarity, but these figures unfortunately give no adequate idea of its frequency in relation to other diseases of the appendix. Few operators make it a rule to have all appendices which they remove examined microscopically. As a rule only those which show to the naked eye some unusual appearance are investigated and thus most of the reported cases have been discovered. Little information concerning the incidence of cancer in a large number of appendices

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examined microscopically as a matter of routine is available. Practically the only series is that of Kelly, who found primary cancer twice in 706 appendices removed at operation. The three tumors here reported occurred in a series of 201 appendices removed at operation and examined microscopically between August 31, 1903, and September 1, 1904.* Previous to September 1, 1903, 320 appendices removed at operation had been examined at the Bender Laboratory, though not always histologically, and as two of Elting's cases were drawn from this number, we have a total of five primary cancers in a group of 521 examinations in one laboratory and representing practically the operations of one hospital (Albany Hospital) for a period of eight years. Moschcowitz's three cases occurred at the Mount Sinai Hospital within a period of sixteen months in a service averaging yearly 200 to 300 operations for appendicitis; all appendices however were not examined microscopically. Neri reports one cancer occurring in a series of eighty appendices removed in Biondi's clinic. It is obviously impossible to draw definite conclusions from these figures. Of the two properly controlled series, Kelly's indicates that cancer occurs in relation to other diseases of the appendix as 1:353, while our series shows a proportion of 1:67. Estimating the other series of cases in the same way, we have for Elting's group a ratio of 1:160, for Moschcowitz's 1:125, while the total number of specimens examined at Bender Laboratory would yield a proportion 1:104. Although these figures vary considerably, it would nevertheless appear justifiable to conclude that routine histological examination of all appendices removed at operation would demonstrate primary carcinoma to be present in about one per cent of all cases.

Etiology.

The only factors worthy of consideration in this connection are sex, age and antecedent pathological conditions of the appendix.

Sex. An analysis of the twenty-seven cases in which the sex of the patient is stated shows that fifteen were females and twelve

*Dr. Pearce tells me that in the following nine months, ending July 1, 1905, 214 appendices were examined at the Bender Laboratory and that but one primary cancer was found.

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males. These figures would indicate that sex is not a predisposing factor, as might appear to be the case from some of the earlier reports which show that three-fourths of the cases occur in females.

Age. One is accustomed to regard carcinoma as a disease of those in or past the fourth decade of life. Carcinoma of the appendix is a surprising exception to this view. Of the twenty-eight cases in which the age is stated, it is seen that all but four of the individuals were under forty years of age and seventeen, or 60.7 per cent., were under thirty.

The largest number of cases in any one decade occurred in the third; the extremes are represented by individuals aged eight and eighty-one years respectively. The first decade is represented by one, the second by five, the third by eleven, the fourth by seven, the fifth by two, the sixth by one, the seventh and eighth by none, and the ninth by one case.

Relation to inflammatory conditions. The frequent occurrence of carcinoma of the appendix as shown by the above analysis in the earlier years of life has been noted by all who have investigated this subject. This has led to the general opinion that the inflammatory lesions of the appendix which occur so commonly in the same period have some etiological relation to the new growth. Letulle and Weinburg especially have emphasized the relation of cancer to chronic obliterative appendicitis. Their view is exceedingly plausible for the appendix is a vestigial organ and it is well known that in such, as well as in atrophied organs, lawless growth of epithelium is prone to occur. Chronic obliterative appendicitis is usually accompanied by some atrophy and considerable displacement of epithelial elements. Under such circumstances irregular growth of epithelium in the midst of the irregular connective tissue proliferation could readily be understood. There is however as yet insufficient evidence to support this view. Aside from Letulle and Weinburg's four cases, in but two is an obliteration of the lumen mentioned and in these it is not clear whether the obliteration preceded or was the result of the new growth. In one of our cases it was impossible to determine this point. In five other cases a definite microscopic diagnosis of chronic appendicitis is made. It is of interest also that a large proportion of the cases give a history of previous attacks referable to the appendix. On the other hand in a larger number of cases the

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tumor gave rise to no symptoms or to but one acute attack. It is obvious therefore, that while it is possible that cancer of the appendix may bear some relation to chronic inflammatory disturbance of the organ, further detailed investigations are necessary before it can be determined whether the latter are the cause or the result of the new growth.

Pathology.

Location of tumor. The location of the tumor is more or less definitely stated in twenty of the descriptions; in twelve it occurred at the distal end usually at the tip of the organ, in three at the base, in two in the middle third and in three it involved the caecum. In these last it is possible that the point of origin was in the caecum.

Gross appearance. The tumor in most instances was obscured by acute inflammation or in an obliteration of the lumen of the appendix and therefore was not recognized upon macroscopic examination; such was the case in each of the three cases here reported. In those reports accompanied by a gross description, the new growth is usually described as a firm white nodule. The size of the tumor varies considerably; the larger ones are described variously as of the size of a marble, a pea or a cherry pit; others measure from five to thirteen millimetres in diameter. Occasionally no distinct tumor is evident but merely a localized thickening of the wall, or more frequently, an obliteration of the lumen indistinguishable from a chronic obliterative inflammation.

Histology. Seventeen tumors have been described as carcinoma simplex, alveolar or spheroidal cancer; in one of these the qualifying adjective, medullary, was used and in one, scirrhus. Eight have been termed adeno-carcinoma or cylindrical cell cancer, two colloid and seven merely carcinoma. The predominating type of tumor therefore appears to be the simple alveolar cancer.

Extension, Metastases and Recurrence. Appendiceal cancer shows little tendency to invade other tissues. Three cases of involvment of the caecum have been reported. In one (Jones and Simmons) the invasion of the caecum was slight; in another (Beger) a tumor the size of a walnut projected into the caecum and metastases were found in the retroperitoneal glands; in

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Elting's case, the adjacent coils of small and large intestine were affected as were also the lymph nodes. With these exceptions, cancer of the appendix appears to have little tendency to extension; the growth being limited as a rule to submucosal and muscular coats. In Norris' case and in Case II here reported a tendency to extend into the meso-appendix was observed. Metastases have been described only in the two cases of Beger and Elting just cited. Little information concerning recurrence of the tumor after removal is available. Few reports contain the after history of the patient and indeed the majority of reports are so recent that sufficient time has hardly elapsed for observations on this point. Rolleston, on account of the poor health of his patient several months after operation, suspected a recurrence. Wier's patient was in good health three years after operation. Harte and Willson quote a personal communication from Hurdon stating that her patient was in good health two years after operation, with no evidence of recurrence. Moschcowitz had occasion to open the abdomen of his first patient one and one-half years after removal of the appendix and found no evidence of recurrence of carcinoma at the site of the previous operation.

Associated Lesions. These include practically all the acute and chronic inflammatory conditions which may affect the appendix. Acute lesions were present in twelve of the cases cited above, and include suppurative, ulcerative and gangrenous appendicitis, periappendiceal abscess and peritonitis. The chronic lesions in thirteen cases include chronic interstitial and obliterative appendicitis, chronic periappendicitis and organization about chronic abscess. Not infrequently acute and chronic lesions were associated. A sinus discharging externally was present in each of two of the cases of periappendiceal abscess. Perforation is noted in two cases. In one, discovered at autopsy, a general peritonitis was present; in the other, at operation, a brownish fluid with faecal odor escaped on opening the peritoneum. Elting's case of colloid cancer, found at autopsy, showed rupture without evidence of inflammation. Enteroliths have been noted in a few instances.

Clinical History. On examination, the clinical data accompanying the cases here recorded shows that appendiceal carcinoma gives rise to no peculiar symptoms; the symptoms demanding operation have in all instances been those of the associated

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acute or chronic inflammation. An analysis gives the following results: Six tumors discovered at autopsy, death being due to other causes, with no history of symptoms referable to the appendix; six discovered while operating for the relief of symptoms referable to disease of the pelvic organs, and twenty-two in which the operation was done on account of symptoms more or less definitely those of appendicitis. Of the latter in two no details of the clinical history are given; in four there is a history of a single sharp attack; in ten a history of recurrent appendicitis with from two to four definite exacerbations and in six a history of symptoms referable to the appendix and covering a considerable period of time. It is worthy of note that in all cases which demanded operation the symptoms were those of inflammation of the appendix. The four cases in which no inflammation was found were among those discovered at autopsy or during operation for disease of other organs. It would seen therefore justifiable to conclude that the tumor itself while limited to the appendix gives rise to no pathognomonic symptoms; all manifestations demanding operation are those of the associated inflammation.

Conclusions.

1. Primary carcinoma of the appendix is present in from one-third to one per cent. of the appendices removed at operation; its discovery at autopsy is very unusual.

2. It is a tumor of early life, occurring usually between the ages of ten and forty; the largest number being in the third decade.

3. It occurs with equal frequency in either sex.

4. Acute or chronic inflammatory lesions are usually present and are responsible for the symptoms demanding operation; the tumor itself while localized gives rise to no pathognomonic symptoms.

5. Direct extension to other organs and metastasis are rare.

6. The usual type is the simple alveolar cancer; adeno-carcinoma occurring next in frequency, while colloid cancer is unusual.

7. Conclusive information concerning the relation of this lesion to other diseases of the appendix can only be obtained by the careful routine histological examination of all appendices removed at operation.

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Reprinted from ALBANY MEDICAL ANNALS, December, 1905.

RETENTION CYST AND DIVERTICULUM OF THE VERMIFORM APPENDIX.

BY ERASTUS CORNING.

(From the Bender Laboratory, Albany, N. Y.)

Retention cyst of appendix.—The recognition of retention cyst, known also as cystic dilation, hydrops and mucocele of the appendix, is generally ascribed to Virchow,[1] who characterizes it as simple cyst caused by the retention of mucus in an organ, partially or completely obliterated in its proximal portion. Virchow, however, refers to Rokitansky's[2] earlier observation that an obstruction of the appendix leads to an accumulation of colloid material and a cystic condition which he terms hydrops of the appendix. Some of the lesions of the appendix reported at about this time as tumor would appear rather to be retention cysts. Virchow states that he considers the colloid tumor described by Gähtgens in 1853 to be such. There is also some doubt concerning the nature of the tumors of the appendix reported by Rokitansky[3] in 1867 as colloid cancer. The gross descriptions of these accurately characterize cystic dilation and in the absence of microscopic examinaton there is reasonable doubt as to whether they are examples of cancer or cyst.

The subject of cystic dilation has never attracted much attention, probably because it is never recognized clinically and also because pathologically it is generally considered to be merely an unusual form of chronic appendicitis. Still the literature contains many reports of cases. Van Hook[4] in 1896 was able to collect thirty-two cases in which the condition was found either at autopsy or operation; a cursory review of the literature indicates that to date only about sixty cases have been reported. The largest number reported by a single investigator are the six described by Ribbert[5] in 1893. Statistics based on autopsy material indicate, however, that it is not very infrequent. Ribbert's cases were found in the course of 400 post mortem examinations. Bryant[6] found one in 124 autopsies, Steener[7] three in

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2,286 autopsies, Boody[8] one in 528, and Christian[9] sixteen in 3,770. These figures, however, give no information concerning the frequency of cystic dilation as compared with other diseases of the appendix as seen at operation and as far as I am aware, no series showing such incidence exists. On this point the records of the Bender Laboratory offer some definite information. During a period of somewhat less than nine years 735 appendices removed at operation have been examined; five or 0.68 per cent. were examples of cystic dilation. These figures and those of Christian, which gave 0.42 per cent. for autopsy material, indicate that this lesion is relatively not infrequent.

The size of the tumor is variable. Virchow mentions a dilation the size of a man's fist; Kelly[10] describes one the size of a small orange; and Guttman[11] one fourteen centimetres in length and twenty-one centimetres in its greatest circumference. As a rule, however, the size is stated to be that of a walnut, a goose egg, a hen's egg or a small sausage. The smaller localized protrusions occasionally described are in all probability divertcula.

The gross appearance of the cyst varies according to the location of the constriction. If the latter is at or near the caecum the cyst appears to be more or less continuous with the caecum and may have a tendency to an erect position. Occasionally the intra-appendiceal pressure may cause the cyst to protrude into the caecum. When the obstruction is some distance from the caecum the cyst has the appearance of a tumor with a pedicle connecting it with the caecum. Very rarely two cysts may develop. The walls may be thick and firm or thin and translucent. Adhesions to adjacent organs are common. The shape of the cyst is as a rule cylindrical, unless the structure is near the tip. Kelly and Hurdon[12] describe an appendix which was seen at operation six years before its removal. At that time in the median portion was a single cyst with obliteration of the lumen beyond. Upon its removal after six years three cysts separated by fibrous partitions had formed; the later ones had developed in the proximal portion. The material within the cyst is, as a rule, a thick gelatinous substance so tenacious that, as Virchow states, it may be picked up with forceps and cut with scissors. As a rule this substance is more or less turbid, but occasionally it is distinctly translucent and of a greenish yellow color. Sometimes thin watery clear fluid or a thicker milky fluid is found. The material may be blood stained. The con-

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sistence of the fluid depends on the functional activity of the mucosa and is therefore an index of the degree of atrophy of the latter. If the cyst becomes infected, suppuration (empyaema of the appendix) may result.

The mucosa is usually smooth and glistening with evidence of atrophy due to mechanical pressure. The finely granular velvet like surface due to the presence of lymphoid tissue is absent. Histologically the picture is that of a chronic inflammation and atrophy. Submucosa and lymphoid nodules have as a rule entirely disappeared. The mucosa is very thin, seldom contains glands and is usually represented by a layer of low columnar or cuboidal epithelium. In the muscular coat fibrous thickening, often hyaline, occurs, and infiltration of lymphoid cells is common. Occasionally small strands of fibrous tissue may bridge the lumen irregularly.

Cystic dilation is usually due to a chronic appendicitis in which, in the process of healing, opposing denuded surfaces become fused together and cause obliteration of the lumen. The secretion in the distal end accumulates and as there is no outlet a cyst results. The following description by A. O. J. Kelly of repair of appendiceal inflammation puts the matter very accurately: "That portion of the wall of the appendix which is the seat of erosion or ulceration is replaced by newly formed connective tissue, which like all newly formed connective tissue, tends to contract and to form cicatricial tissue. As a consequence the lumen becomes contracted. If there have been several points of ulceration, there will also be several points of stenosis of the lumen. Depending upon the situation, size, and shape of these cicatrices, there results either a transverse narrowing of the lumen, or, particularly if the cicatrix be longitudinal rather than annular, there will ensue a shortening of the organ along one side—a curling up of the appendix, or an angulation, flexure, twist, etc. If there be several cicatrices, the utmost distortion of the appendix may be produced. On the other hand, there may be complete obliteration of the lumen of the appendix at one or more points along its length. It is readily conceivable that in the event of annular ulceration, granulating surfaces being everywhere opposed to granulating surfaces, these adhere, and, as the processes of regeneration and organization go on, become permanently united by means of newly formed connective tissue. Such obliteration of the lumen may be circumscribed or general-

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ized. In the latter case obliterating appendicitis results; in the former merely a local obliteration. The latter may be situated anywhere, and not uncommonly gives rise to a condition known as cystic dilation, retention cyst, hydrops, or mucocele (Fere) of the appendix. The development of this condition of cystic dilatation of the appendix depends upon several factors. The obstruction of the lumen must be complete, or almost so: the obstruction or obliteration must have obtained at a time when the affected portion of the organ contained no pathogenic micro-organisms, the mucus membrane of the affected portion must be intact, or at least capable of functionating; and the secretion by the mucus membrane must be more rapid than the absorption from the portion of the appendix involved. If the obstruction be not complete, the secretion is likely to be forced through even a narrow opening with sufficient rapidity to prevent a large accumulation, and, on the other hand, infection is likely to occur through the patulous lumen, converting a cystic dilatation into an empyaema. If there are already virulent bacteria in the affected portion of the appendix, an empyaema, of course, rather than a cystic dilatation, will develop in the first place. If the mucous membrane is incapable of functionating, there can be no accumulation of fluid, and the same is also true if absorption be more rapid than secretion."

It is a matter of interest that in a case reported by Gruber[18] a tuberculous ulcer apparently aided in bringing about complete stricture of the appendix.

It is obvious that it is only in connection with inflammatory obliteration of the lumen—a formation of synechia similar to that seen in various cavities of the body—that retention cyst can develop. It cannot develop in that form of obliteration which Ribbert and others regard as an involution process in a vestigial functionless organ for in such appendices the obliteration begins at the tip and gradually involves the entire organ; there is, under such circumstances, no possibility of the retention of secretion.

Not all cases, however, are due to obliteration of the lumen. A cystic condition may be caused, as in the case reported by Treves and Swallow by a twist, kink or angulation of the appendix. Periappendiceal adhesions may assist in maintaining such a condition.

Other forms of cyst as the hydatid reported by Lafforgue and

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the subserous cyst mentioned by Christian do not come within the scope of this communication.

Clinically, cystic dilation gives rise to no pathognomonic symptoms and the condition is usually mistaken for some other form of appendicitis or is discovered accidentally. A palpable tumor in the right iliac fossa, as in the cases of Wier[15] and Landenberger[16] should, in the absence of acute symptoms, cause retention cyst to be considered. Aside from this the symptoms are usually obscure or suggestive of chronic appendicitis. Wood[17] has called attention to the possibility of mistaking the tumor for floating kidney and also to the danger of rupture by taxis when the cyst is in an inguinal hernia. Such an accident is reported by Van Hook. Wölfer and McArthur[18] each report a case of cystic appendix in the sac of a hernia.

There appears to be no relation between cystic dilation and cancer of the appendix, though both have an interesting relation to obliterative lesions. In a small proportion of the cases of cancer the tumor develops in an obliterated portion of the appendix, usually the tip of the organ. Obliteration at this point is, however, as a rule that due to involution rather than to inflammation. The only cystic carcinoma limited to the appendix, is the case of colloid cancer reported by Elting,[19] if we exclude Rokitansky's cases, which in the absence of microscopic examination appear to be retention cysts. On the other hand Elting's tumor appears to be a primary lesion, for in the description, no mention is made of an obliteration of the proximal portion of the appendix. Furthermore, in cystic dilation the changes in the epithelial cells are those of atrophy rather than of proliferation.

Diverticulum of the appendix.—The condition known as diverticulum of the appendix has attracted but little attention. Ribbert appears to have been the first to report this conditon. He describes a retention cyst on the surface of which, at the mesenteric border, was a group of small cysts which he considered to be caused by the cystic dilatation of glands in the mucosa. Kelynack[20] reports a somewhat similar condition in which two diverticula were directed beneath the folds of the mesentery. Hawkins mentions an appendix with five or six diverticula. Kelly and Hurdon refer to a case in which the diverticulum was associated with retention cyst. Edel,[21] Fischer,[22] and Hedinger[23] each report single cases of diverticulum; Lejars and Menetrier,[24] two cases; and Mertens,[25] three cases in a series of 139 specimens examined.

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In the cases above quoted, cystic dilation of the appendix existed in four, cancer in one, and tuberculosis in one. Periappendicular adhesions are frequently mentioned. Lejars and Menetrier describe an acute inflammation affecting the diverticula in one of their cases; to this condition they give the name of "appendicite diverticulaire." The size of the diverticula varies. In some cases they were found only on histologic examination; in others they are small nodular protuberances on the surface of the appendix. Lejars and Menetrier describe them as hemispherical elevations varying in size from that of a raisin to a small pea. The largest apparently is that of Fischer, which measures 11 x 12 millimetres.

It is a general rule that diverticula of various portions of the intestine occur in individuals past middle life; to this rule diverticulum of the appendix is not an exception. The age is given in seven of the twelve cases collected by Hedinger; in five of these it varied from sixty-six to seventy-five; in one it was forty-seven and in another fifteen. Ribbert states that the lesion which he reports occurred in an old man, while Fischer's was in an individual about fifty. On the other hand the appendix described by Hedinger was that of a newly-born child.

Most if not all of the diverticula of the appendix belong to the group of false diverticula, that is, they are a protrusion of the mucosa and submucosa through the muscular coat. The wall of the sac therefore has no muscular coat thus differing from true diverticula in which all coats are represented. False diverticula, as far as is known, are acquired and never congenital. It is of interest therefore to consider the conditions in the appendix which may be concerned in the etiology of diverticula. The association of obstructed lumen and cystic dilation in five of the cases, including the one here reported, strongly supports the theory which ascribes the chief influence to increased intra-intestinal pressure; in this instance, of course, intra-appendiceal pressure. Likewise the frequency with which the processes penetrate the mesentery supports those observations which indicate that the diverticulum forms at the point of least resistance, that is along the sheath of a blood vessel (vein) passing from the intestine into the mesentery.

Traction is not believed to be a common cause of diverticulum though true diverticula of the intestine have several times been described as the result of traction exerted by accessory pancreas

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or connective tissue bands. Such traction on the appendix associated with inflammation, or the pressure of faeces, might lead to pressure atrophy of the mucosa and muscularis and a condition analagous to false diverticulum.

That diverticulum of the appendix may be congenital has been definitely determined by Hedinger's observation of the condition in a newly-born child.

Report of Cases.

The records of the Bender Laboratory covering a period of nine years contain descriptions of 735 appendices removed at operation; among these are found four examples of cystic dilation, with also, in one, a peculiar form of diverticulum. Other diverticula of lesser degree may have occurred during this period, but if so have not been sufficiently characteristic to attract attention. The descriptions of these appendices follow:

Case I.—Records of the Bender Laboratory, Surg. Path. No. 49:60.

Clinical History—Mr. B., aged 16, admitted to the Albany Hospital Service of Dr. W. G. Macdonald, February 16, 1900. *Past history*—Negative. *Family history*—Negative. *Present illness*—Six weeks ago and again three weeks ago well-marked attacks of appendicitis, the second lasting two weeks. Attacks began with diffuse pain, starting in the region of the stomach, finally localizing in the right side. *Clinical diagnosis*—Chronic appendicitis. *Operation*—February 17th; uneventful recovery; discharged March 3d, cured.

Pathological Examination.—Gross Description—The specimen consists of an appendix removed at operation. It is 6 cm. in length; the proximal portion for a distance of 3 cm. averages 7 mm. in diameter; the distal half is much enlarged, and measures from 13 to 16 mm. in greatest transverse diameter. The vessels of the peritoneal covering are much congested. The enlarged distal portion is distinctly cystic and on pressure a small quantity of mucoid material can be expressed through the narrowed lumen of the proximal portion of the appendix. The dilated portion of the appendix is found to contain a considerable amount of gelatinous mucoid material. On the side opposite the mesenteric attachment, the walls of the appendix are distinctly hypertrophied and the mucous membrane is thickened. Along the mesenteric attachment in the upper portion of the cystic enlargement the walls of the organ are greatly thinned and at one point is a minute opening 2 mm. in diameter, which is plugged with mucoid material. On this side of the appendix the mucosa appears to be entirely atrophied for some distance. A similar atrophy of the muscular coat over a small area is also evident. Again at a lower point the material in the lumen of the appendix appears to have destroyed by pressure all portions of the wall except the peritoneal coat

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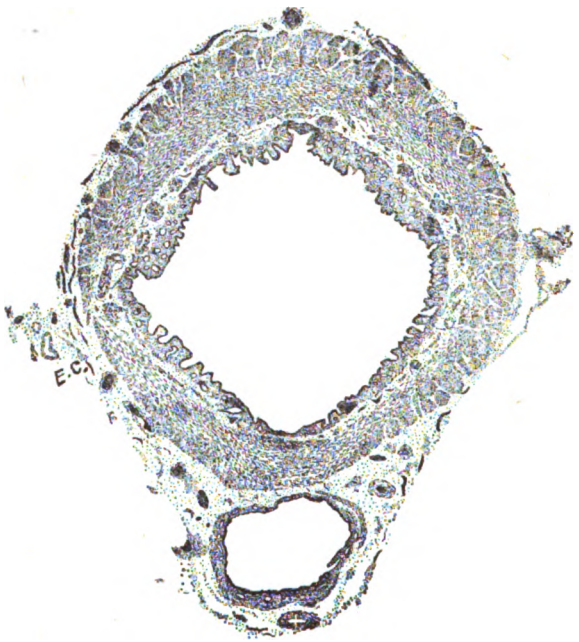
and has separated the peritoneum from the muscle for a short distance, forming a small cystic cavity 4 mm. in diameter, the walls of which are somewhat irregular. At a point 14 mm. from the beginning of the dilation of the appendix the lumen rapidly narrows until it measures but 2 mm. in diameter. This condition extends for a distance of about 4 mm., when the lumen again enlarges to form a dilation 8 mm. in length, and 7 mm. in transverse diameter. The walls surrounding this area of dilation are hypertrophied and the mucous membrane in some places is somewhat thickened, in other places apparently atrophied. Toward the tip of the appendix the dilation of the lumen ceases; the lumen of the extreme tip is obliterated.



Illustrates lesions of Case I. Larger cavity is that of cystic appendix with marked atrophy of mucosa and submucosa; smaller cavity is the diverticulum in the mesentery. (x 6.)

Anatomical Diagnosis—Chronic appendicitis with cystic dilation of distal end.

Histologic Description—Sections through four different levels of the cystic dilation were studied. Unfortunately no sections were taken through the constricted portion. To the naked eye sections from each level show in the attached mesentery a circular opening, which at first glance apparently a blood vessel, proves when placed under the microscope to be a cavity lined by a mucosa similar in every respect to that of the appendix proper. This diverticulum varies in diameter in the hardened and stained preparation from 0.15 to 0.35 cm; its form is almost uniformly circular though occasionally oval.

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The lumen of the appendix proper is dilated, and that portion of its wall most distant from the mesentery is much thickened. The lumen is free except for small masses of mucoid material adherent here and there to the mucous membrane. The character of the latter varies at different levels, but atrophy is everywhere a prominent feature of the lesion. The surface epithelum is of the cylindrical goblet cell type and forms an unbroken ring about the entire circumference of the appendix. This surface epithelium is directly continuous with that of the glands opening into the lumen. These glands are all lined by the same tall cylindrical cells with clear periphery. Many of the glands are small and irregular; others are dilated, forming small cysts in the mucosa. Opposite the diverticulum they have almost entirely disappeared. The interglandular tissue of the mucosa is rich in eosinophiles. The lymphoid nodules are very small, appearing usually as narrow elongated patches; on the mesenteric side they are entirely absent. The submucosa is very indistinct and slightly infiltrated with lymphoid cells and eosinophiles, as are also the muscular coats and the subserous tissues. The blood vessels of the latter are numerous and greatly congested. On the mesenteric side, between the diverticulum and the appendix proper, the muscular coat is much thinner than on the opposite side.

The diverticulum lies outside the muscular coat in a loose vascular adipose tissue freely infiltrated with lymphoid cells. The mucosa of the diverticulum is very similar to that of the appendix itself, though the glands are smaller and fewer in number, and the surface epithelium is not so markedly of the "goblet cell" type. A delicate muscularis mucosa, and submucosa are evident, as are also a few small accumulations of lymphoid cells, which however bear no resemblance to lymph follicles. Eosinophiles are numerous. No muscular coat can be seen at any level; the diverticulum is thus of the type characterized as false.

Microscopic Diagnosis—Chronic appendicitis with cystic dilation and false diverticulum.

By comparing the gross and histological appearances it is apparent that this diverticulum ran through the greater portion of the cystic dilation. Unfortunately owing to the fact that it was not recognized upon gross examination its exact length and its mode of termination cannot be determined. It appears justifiable to conclude that the small opening plugged with mucus at the upper portion of the dilation noted in gross examination was the point of origin. From here it passedapparently through the muscular coat and instead of protruding any distance into the meso-appendix, passed downwards in close relation to the muscular coat. As it is seen in four different sections taken at various levels of the dilation it must have passed almost to the tip of the organ which would give it a length of about three centimetres. Whether it terminated blindly or communicated

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again with the lumen of the appendix cannot be determined. The possibility of the latter is suggested by the small irregular dilation of the end of the appendix noted in the gross description.

Case II—Records of the Bender Laboratory. Surg. Path. No. 49:76.

Clinical History—Mrs. G., aged 50, patient of Dr. Albert Vander Veer, Albany Hospital. *Family history*—Negative. *Past history*—Always more or less constipated. *Present illness*—For the past three or four years has had colicky pains in right lower abdominal region. Three months ago the patient had a well defined attack of appendicitis, with constipation, pain and vomiting. Enemata were given, and the patient made a good recovery. An operation was advised, but postponed temporarily.

Operation by A. Vander Veer, December 26th. On opening the abdominal cavity, a small amount of serous fluid escaped. The appendix was found back of the caecum and bound down by adhesions.

Pathological Description.

Gross Description—Specimen consists of the distal 3 cm. of an appendix. The proximal end has very thick walls and the lumen is almost entirely obliterated for a distance of 5 mm. Below this the organ is enlarged, averaging 14 mm. in diameter. There are a few adhesions over the serous surface. The peritoneum is injected, and there are a number of discrete and confluent pin-point subperitoneal haemorrhages. At one place the wall is thin, and presents a perforation 3 mm. in diameter with irregular edges. (This perforation was produced artificially after removal of the appendix.) On section the mucous membrane of the distal 2.5 cm. is pale and covered with a yellowish, almost transparent jelly-like colloid material. The remainder of the mucous membrane is smooth and free from this material. The walls of the organ are considerably thickened. The musculature averages 4 mm. in thickness. In the neighborhood of the perforation the wall is very thin, the mucous membrane and musculature have entirely disappeared over an area 4 mm. in width. The mesentery, which accompanies the specimen, is deeply congested.

Accompanying the specimen was a large mass of colloid material, yellowish red in color; and distinctly striated. The reddish color present is apparently due to the presence of blood or blood pigment.

Anatomical Diagnosis—Chronic obliterative appendicitis with cystic dilation.

Microscopic Description—A section through the proximal end shows the normal structures of the appendix to be entirely obliterated by a chronic inflammation, which leaves only a narrow slit-like opening lined by a very low cylindrical epithelium. The glands and lymph nodules have been entirely destroyed, and the submucosa has been replaced by a dense connective tissue more or less hyaline in character. The muscular coat is very thick and replaced in part by fibrous tissue. Lymphoid cells are numerous throughout all coats. The serous coat is thickened and adherent to it are numerous vascular fibrous tags. In the submucous, muscular and serous coats of a lower level is seen the same chronic

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inflammatory condition as in previous section. In the center of the section is an irregular lumen much smaller than normal, which contains blood stained colloid material. The mucosa consists of low irregular papillary projections lined by three or four layers of cylindrical cells; no glands are present.

A section through the point of greatest dilation shows an area of chronic ulceration in intimate contact with the colloid contents of the lumen. The colloid material which stains deeply with haematoxylin is clear and hyaline with a more or less stratified arrangement, and contains no cells.

Case III—Records of the Bender Laboratory, Surg. Path. No. 49:212.

Clinical History—Mr. D., aged 36, admitted to the Albany Hospital, service of Dr. Albert Vander Veer, on June 9, 1902. *Family and past history* negative. *Present illness*—Attacks of sudden abdominal pain in August, 1901, and four similar attacks since. Now presents symptoms of acute appendicitis. Operation June 10th; appendix deep in pelvis and firmly bound by adhesions.

Pathological Examination—Gross description—Specimen consists of the distal portion of the appendix vermiformis, and is 4 cm. in length and irregularly distended. The outer wall is roughened with blood stained fibrous adhesions. The diameter of the tube at proximal end is 1.5 cm. On section the lumen of the appendix is found to contain a colloid substance, which can easily be expressed; the wall is thickened. The mucous membrane appears thickened and oedematous, and near the tip the mucous membrane forms a small pouch-like dilation, which is filled with colloid material.

Anatomical Diagnosis—Chronic appendicitis with localized cystic dilation.

Histological Examination—Two sections through proximal portion of the appendix show evidence of chronic inflammation involving all coats of the organ. The serosa is thickened, and to it are adherent numerous vascular tags of fibrous tissue. The mucosa is atrophied and contains a few small irregular glands widely separated; the surface epithelium has almost entirely disappeared; the lymphoid nodules are small and irregular. The lumen contain a colloid material with fragments of desquamated epithelial cells. A section through the dilated portion shows the same general condition, and in addition, a cavity 4 mm. in diameter between the muscular and serous coats. This latter cavity contains a material which is similar to that in lumen of appendix, but is richer in cell debris and contains red blood corpuscles. Its epithelial membrane has almost entirely disappeared, but here and there are small accumulations of cuboidal epithelium; no glands are evident. The surrounding tissue is freely infiltrated with lymphoid and plasma cells and a few polymorphonuclear leucocytes. Much old blood pigment is present. This cavity is apparently the periphery of the cystic dilation mentioned in the gross description; unfortunately, the section does not pass through opening into appendix proper.

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This case presents a few points of peculiar interest. No cause for the retention of secretion was evident either upon gross or histological examination. A constriction may have existed at the junction of appendix with caecum, or a twist may have been present. Unfortunately the clinical notes contain no reference to the conditions found at operation other than that the appendix lay in the pelvis and was bound down by adhesions. The histological picture, however, justifies the diagnosis of cystic dilation. The small pouch at the distal end must be considered as a false diverticulum. In view of the observations of Lejars and Menetrier concerning "diverticular appendicitis" it is of interest that in this pouch we have an ulcerative inflammation which though of a chronic character is more active than that in the appendix proper.

Case IV—Records of the Bender Laboratory, Surg. Path. No. 04:123.

Clinical history—Mrs. H. T., aged 60, admitted to the Albany Hospital, service of Dr. A. W. Elting, February 18, 1904. *Family history*—Father living. Mother died at 22 after amputation of knee for tuberculosis. *Past history*—Had pneumonia in 1891. Has had two living children and one miscarriage. Always had painful menstruation. Menopause at 47. *Present illness*—About 25 years ago patient noticed a pulsating tumor in median line of abdomen, and on exertion had severe pain in epigastrium and thorax with dyspnoea. At the same time she had occasional attacks of vertigo, but never became completely unconscious. In August, 1903, she was confined to bed for three weeks after severe attack of pain in the abdomen. At this time the pulsation disappeared, though swelling remained in median line of hypogastrium. There was difficulty in micturition and defaecation. Micturition was frequent. Appetite good. No history of vomiting.

Patient on admission was found to be a very small framed, poorly developed and poorly nourished woman. Skin and mucous membranes pale. Pulse 100; low tension; poor quality. Wall of artery somewhat thickened. Lungs slightly emphysematous. Heart negative. Abdomen decidedly prominent, particularly in the lower portion. Prominence appears to be symmetrical, and seems to emerge from the pelvis. On palpation a large tumor mass can be felt, which apparently occupies the entire pelvis and projects upward to about the level of the umbilicus. This tumor is of rather firm consistence and somewhat irregular outline. It does not appear to be at all moveable. There is some tenderness on palpation over the tumor. Distention of the intestines is evident, and the action of the bowels has been extremely sluggish. *Operation,* February 20th. Median incision between the umbilicus and pubes exposes a cyst lying in the pelvis and found to be adherent to adjacent structures. On opening the cyst about 1,000 cc. of semi-solid gelatinous material can be removed. Left tube and ovary removed. Dilated appendix with a

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portion of caecum, supposed to be a colloid cancer of the appendix, dissected away.

The patient recovered satisfactorily from the shock of the operation, and her convalescence was uninterrupted.

Pathological Examination—Gross description—Material received as two separate specimens. Smaller specimen is an appendix, the distal end of which is enlarged to form a globular cyst 3.5 cm. in diameter. The proximal portion 3.5 cm. in length has an outside diameter of from 0.8 to 1.2 cm., and has a patent lumen. The entire specimen is covered with blood stained fibrous tags. The wall of the cystic portion is 2 mm. in thickness, while that of proximal portion measures 3 mm. The cyst contains an amber colored jelly-like material. Specimen not further examined, but placed in fixation fluid.

Larger specimen consists of approximately 1,200 cc. of thick dark amber mucoid material and a collapsed cyst wall. The latter when distended measures 14 cm. in its greatest diameter. Its wall is 1 to 2 mm. in thickness. Attached to this piece of cyst wall by bands of fibrous tissue is a portion of normal Fallopian tube 6 cm. in length.

Anatomical Diagnosis—Colloid cyst of appendix. Unilocular cyst of ovary. Normal Fallopian tube.

Microscopical Description, Appendix—Lumen greatly dilated. Mucosa and submucosa atrophied. Mucosa is so stretched that tubules are very shallow or entirely obliterated, and form a continuous layer with irregular projections into the submucosa. No isolated glands are present. The epithelial cells are elongated, compressed and practically all of the goblet cell type. In some places the glandular appearance is entirely lost, and the lining epithelium consists of but a single layer of low cuboidal cells. The lumen is filled with an almost homogeneous hyaline material, which stains faintly with haematoxylin. The lymphoid nodules are atrophied and few in number. The muscular coat shows increase of connective tissue and slight infiltration of lymphoid cells.

Microscopic Diagnosis—Colloid retention cyst of appendix.

In this case as in the previous one the cause of the retention is not apparent. The portion of appendix received from the surgeon showed the lumen of proximal end to the patent and the description of the operation makes no mention of obstruction. It is possible that the large ovarian cyst may, by pressure, have caused an obstruction or kink of the appendix, but on this point there is no information.

The following case of colloid deposit about the appendix, though it illustrates neither cystic dilation nor diverticulum, is believed to be of some interest because of the possibility of confusing it with a ruptured cystic appendix.

Records of the Bender Laboratory, Surg. Path. No. 58:119.

Clinical History—Mrs. B., aged 40, admitted to the Albany Hospital, service of Dr. W. G. Macdonald, on September 2, 1903. *Family history*—

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Father and brother died of tuberculosis. No history of cancer. *Past history*—Patient had the usual diseases of childhood. Her menstruation began at 13, and has always been regular. She had two children and one miscarriage. She had "inflammation of the bowels" at the age of 12 years. At the age of 20 she was troubled by bleeding from the bowels. For the past two years patient has suffered from indigestion. She has always been more or less constipated. *Present illness*—On the 28th of July the patient felt perfectly well and spent most of the morning out of doors. She ate a hearty dinner, and at three o'clock in the afternoon was taken ill with severe pain in the right iliac region. At this time she vomited once. In a short time she complained of pains throughout the abdomen. At midnight she took an enema with good results. The next day a physician was called, who made a diagnosis of chronic appendicitis with pelvic inflammatory disease, and advised operation.

Operation, September 3d, by Dr. W. G. Macdonald. Incision in the median line between the symphysis and umbilicus. The appendix was found bound down by adhesions. There was an ovarian cyst on the right side. Operation consisted of repair of the cervix, curettment of uterus, clamp cautery for haemorrhoids, right salpingo-oöphorocystectomy and appendectomy.

Pathological Examination—Gross description—Material to be examined consists of appendix and Fallopian tube with broad ligament.

The appendix is of normal size with mesentery attached. The peritoneal surface is blood stained and congested. All coats are greatly thickened; the mucosa is swollen. At tip, externally, is an accumulation of thick colloid material intimately adherent to appendix and apparently covered by peritoneum. No evidence of rupture or perforation.

The Fallopian tube is swollen, and its walls thickened, its peritoneal surface injected, and its lumen contains a thin purulent fluid. Near distal end in the broad ligament is a thin walled cyst 6 cm. in diameter, containing clear slightly yellow mucoid fluid. Ovary absent.

Anatomical Diagnosis—Colloid mass about tip of appendix. Cyst of broad ligament; chonic salpingitis.

Microscopic Examination—Appendix—The mucosa and submucosa are normal. The muscular coat appears to be greatly thickened. Intimately adherent to the serosa, and equalling the section of the appendix in size, is a roughly circular mass of colloid material taking a faint haematoxylin stain. This mass is partially organized, having an alveolar appearance, due to septa of new formed connective tissue. Numerous new formed blood vessels penetrate the mass at various angles, and there is considerable infiltration with lymphoid cells and polymorphonuclear leucocytes. Adherent to this mass and connecting it with the appendix, as well as to the adjacent adipose tissue, are strands of newly formed connective tissue.

Fallopian tube—Lumen contains pus cells and granular material. Papillary processes largely destroyed; those remaining are infiltrated with lymphoid cells and leucocytes. This infiltration extends through all the coats. The serosa is thickened and edematous.

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Microscopic Diagnosis—Organizing mass of colloid adherent to appendix. Chronic salpingitis.

At first glance the condition just described was supposed to be either a ruptured colloid cyst of the appendix or a colloid cancer. Careful gross examination ruled out the first and microscopic examination the latter. The absence of either acute or chronic inflammation of the inner coats of the appendix would contraindicate an explanation based on the supposition of a previous rupture. The appearance of the mucosa was not that of retention cyst. It is apparent, therefore, that the material about the appendix can be considered only as an accumulation resulting from the rupture of a colloid cyst elsewhere in the abdomen. A cyst of the ovary or broad ligament would appear to be the most probable source. The operator noted a cyst on the right ovary and the gross examination of the tube revealed a cyst of the broad ligament. It is possible that a third cyst, which in its collapsed state, escaped observation may have been the source of the colloid material. The sudden attack of severe abdominal pain, in the absence of previous symptoms, is very suggestive of the rupture of a cyst with the escape of its contents into the abdominal cavity. The degree of organization in and about the colloid material was about what would be expected in the period which had elapsed.

Rupture of ovarian cysts leading to interesting secondary lesions in the abdomen, although by no means common, is a well understood condition. The localization of the cyst contents about the appendix and its discovery at operation are, however, very unusual.

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Reprinted from ALBANY MEDICAL ANNALS, November, 1905.

THE ELIMINATION OF ENDOGENOUS URIC ACID IN A CASE OF CHRONIC GOUT.*

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During the past few years as the result of numerous investigations of uric acid metabolism, views concerning uric acid formation have been greatly modified. The theory, once almost universally accepted, that in mammals, uric acid is a product of the metabolism of all albumins and represents a stage preceding the formation of the end-product, urea, has been abandoned. A considerable number of definite new facts has been established and new theories have been brought forward to explain them.

Only a brief summary of the more important points in regard to this work will be given here. For more complete information and for references to the extensive literature the reader is referred to reviews by Baumgarten, Futcher and others.[1]

According to recent views the uric acid eliminated by the normal human body when the individual is on a mixed diet is from two sources; that from the food, which is called the "exogenous" uric acid; and that from the metabolic processes of the individual which is known as "endogenous" uric acid. The same terms, first used by Burian and Schur,[2] apply also to the bodies closely related to uric acid known as the xanthin or purin bases. Uric acid and purin bases together are called "purin bodies" or "purins." It is stated[3] that of the purins eliminated in the urine

* Published also in *American Medicine*, 1905, x, 315.

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nine-tenths are present as uric acid and one-tenth as purin bases. Kaufmann and Mohr,[3] however, find variations in the relations of uric acid to total purins.

As a result of the work of Mares,[4] Horbaczewski,[5] and others, the exogenous purins in the urine of mammals are believed to arise, not from the decomposition of all albumins, but only from the nucleins and the preformed purins which they contain. The other nitrogenous elements of the food are said to produce no uric acid or purin bases in the urine.

More recent investigations, particularly those of Burian and Schur,[6] Siven,[7] and others, have led to general conclusions regarding the formation and elimination of exogenous and endogenous uric acid. The validity of some of these conclusions may fairly be questioned.

According to these investigators the endogenous uric acid and purin bases found in the urine arise from metabolic processes which go on independently of the amount or composition of the food, *e. g.*, from the destruction of the nuclein of body cells.

Burian and Schur have also claimed that the exogenous and endogenous uric acid and purins found in the urine of man can be separately and accurately determined. From analysis and experiment they conclude that the following articles are practically free from nuclein causing uric acid elimination: milk, cheese, eggs, white bread, butter, rice, lettuce, cabbage and potatoes. Such a diet they call a "purin-free diet." They consider that the uric acid eliminated by an individual on a purin-free diet is derived exclusively from endogenous sources. They have also attempted to analyze accurately articles of food rich in nucleins that produce purin elimination. Such foods are thymus, liver, pancreas, spleen, kidney, and among the vegetables, peas and beans. The extractives from muscle also contain nuclein.

It has been contended by Burian and Schur and others that the endogenous uric acid normally eliminated by man on a purin-free diet is a constant quantity for each individual, but that this may vary in different individuals. In one individual the value of the daily endogenous uric acid elimination was found not to vary more than 0.03 grams in determinations made at different times in a period of 18 months. In different individuals it varied from 0.2 grams to 0.7 grams. It is stated that this constant value represents the minimum amount of uric acid excreted by the

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individual; that the constant figure indicates normal metabolism; that its increase points to increased cell destruction going on in the body. The statements in this paragraph apply only to uric acid metabolism in health.

From experiments the conclusion has been drawn that it is also possible, when a person is on a mixed diet, to determine what portion of the uric acid elimination is endogenous and what portion is exogenous. The degree to which the foods rich in nuclein and preformed purins cause uric acid elimination is said to depend not on the individual, but on the amount and kind of food ingested. For example, it is claimed by Burian and Schur that about 50% of the amount of uric acid or other oxypurins taken into the body with the food under normal conditions is constantly eliminated as uric acid, and that while the remaining 50% may undergo further decomposition in the course of metabolism, being changed into other products, this certain definite portion is eliminated unchanged. This would give a method for determining the exogenous portion of the uric acid elimination, providing the nuclein content of different foods could be accurately estimated. If the metabolism of exogenous and endogenous uric acid were carried on in the same way and in accordance with this law, the endogenous uric acid eliminated in the urine would represent 50% of that normally formed by the metabolic processes of the body independently of the food. Variations from these proportions would show that the metabolism was not normal and the degree to which the body could eliminate, as uric acid, the purin bases taken with the food would indicate the degree to which it could oxidize the uric acid arising in itself.

These views regarding uric acid metabolism in health are largely the result of the experimental studies of Burian and Schur, and Siven and have been somewhat widely accepted. They have also been made the basis of some few studies with regard to uric acid metabolism in disease, and especially in gout. The studies of Vogt and others[8] lead them to the conclusion that in gout the exogenous purins are more slowly excreted than in health. Kaufmann and Mohr[9] have published studies which indicate that the values of both endogenous and exogenous uric acid between attacks are within normal limits. It is generally admitted that in the acute gouty attack there is constantly a greater excretion of uric acid than in the free intervals, and that probably it is preceded by diminution. When attacks follow each

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other irregularly the picture becomes confused. There has been considerable discussion as to whether the curves of the uric acid and of the phosphoric acid excretion are parallel in gout, but the matter cannot be said to be entirely settled.

The present investigation was undertaken for the purpose of obtaining, if possible, further information on these points.

The case here reported is one of chronic gout in which a few urinary tests were made while the patient was on a purin-free diet. The first series of analyses cover a period of 10 days. The 24-hour quantity, the specific gravity, and the daily amount of uric acid and of phosphates were determined.

The uric acid was determined by the Folin-Hopkins method, and the phosphoric acid by titration with uranium nitrate. The conditions under which the patient lived were constant as regards exercise (which consisted of light work about the ward) and sleep. Movements of the bowels occurred regularly. The urine was collected and kept in a large stoppered bottle in the bathroom of the ward until the 24-hour amount was obtained, and then placed on ice. The room temperature varied from 72° F. to 85° F.

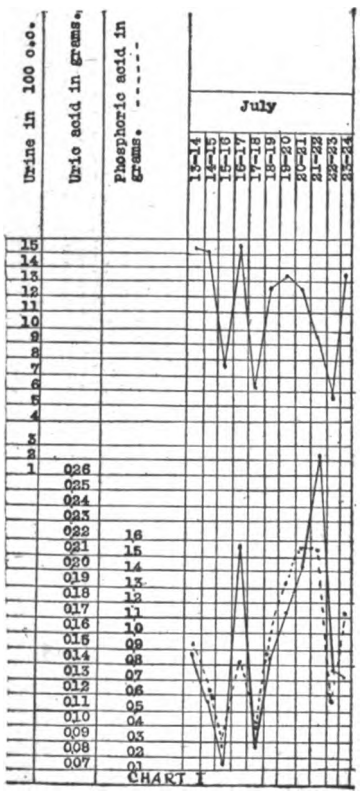

CHART I

Case.—C. F., male, aged 52, gardener and storekeeper, American, was admitted to the Albany County Hospital, October 23, 1902, complaining of swollen joints of hands and feet. His father was born in England, used alcohol freely; mother still living, born in this country of English parents. Her people used liquors freely. There is no family history of gout or rheumatism.

The patient has used alcohol all his life. Ale has been his favorite beverage. He has always eaten freely, especially of meats and sweets. He has never been compelled to do much hard work. The first attack of gout affecting the great toe of the right foot, occurred about 12 years before his admission to the hospital. Since then he has had recurring

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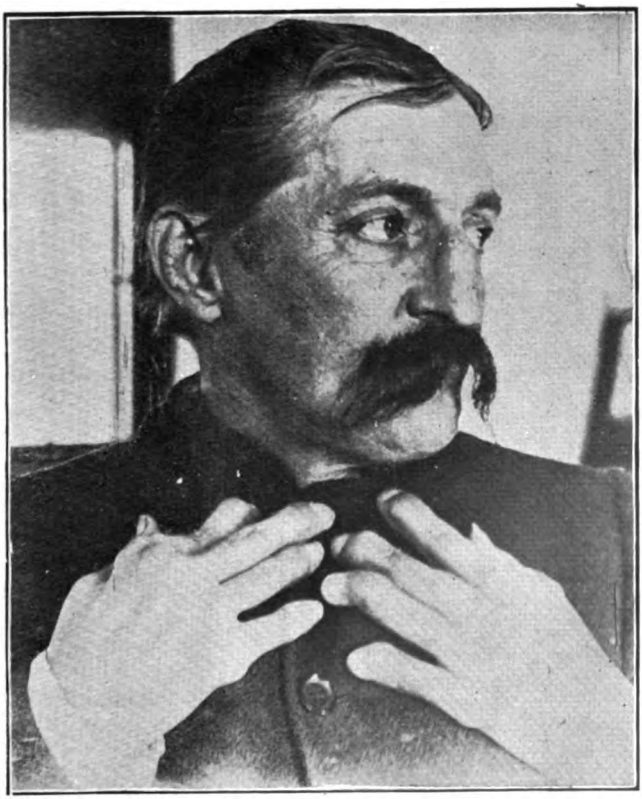
To Illustrate Dr. Laird's Article on "The Elimination of Endogenous Uric Acid in a Case of Chronic Gout"

Albany Medical Annals, November, 1905



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similar attacks in various joints. The joints of the fingers and toes have repeatedly become swollen and now tophi may be seen in the fingers, toes, heels, in both ears, and on the nose. Physical examination of the chest is negative as regards the lungs; the heart is enlarged and aortic murmurs, both systolic and diastolic, are heard. The urine contains a trace of albumin, and a few hyaline and granular casts, but no sugar. Clinical determinations of urea by the Doremus method give uniform low values, 8 grams to 26 grams per day. Leukocyte count July 15, before dinner, 6,000.

The tests were commenced July 13, 1904. At first the diet was not modified, and consisted of oatmeal and milk for breakfast; tea, bread, and vegetables for dinner, and bread and tea for supper. As the patient ate no meat, it was practically a purin-free diet. July 19 he was put on the following purin-free diet: breakfast consisted of white bread and milk, with an egg; dinner was the same as breakfast; supper consisted of bread and milk.

TABLE I.

Date. 1904.	Urine in cc.	Specific gravity.	Uric acid in grams.	Phosphoric acid in grams.	Remarks.
July 13–14...	1520	1010	0.149	0.912	Patient feeling well; temperature normal; about ward.
" 14–15...	1505	1011	0.116	0.622	
" 15–16...	770	1010	0.075	0.269	
" 16–17...	1540	1010	0.219	0.800	No marked pains.
" 17–18...	620	1010	0.087	0.372	
" 18–19...	1265	1009	0.142	0.875	
" 19–20...	1335	1010	0.173	1.33	
" 20–21...	1260	1010	0.205	1.575	Severe pains in several joints; temperature, 100.6°.
" 21–22...	970	1010	0.271	1.57	Patient in bed.
" 22–23...	550	1011	0.138	0.583	Feeling better today.
" 23–24...	1335	1012	0.132	1.140	Feeling well; out of bed.

The patient was about the ward and able to help in light work, though suffering some slight pain, until the early morning of July 21 (2 a. m.), when he began to have severe pains in the fingers, shoulders, and hips. His temperature, which had previously been normal, rose to 100.6° at 7 a. m. He remained in bed during the day, and by night the pains had become less severe. On the morning of July 22 the house physician prescribed wine of colchicum, of which the patient received 18 drops on July 22, and also the same amount on July 23 and 24. On July 24 he was out of bed.

Table I and Chart I give the total amount of urine in 24 hours, the specific gravity, uric acid, and phosphoric acid.

The second series of analysis covered a period of about 22 days. On four days (August 25, 26, 27, and September 3) no tests could be made. The urine was collected in stoppered bottles and put, as soon as passed, on ice, in a small refrigerator placed in the ward for that purpose, and it remained on ice until the tests were made. (The fact that the

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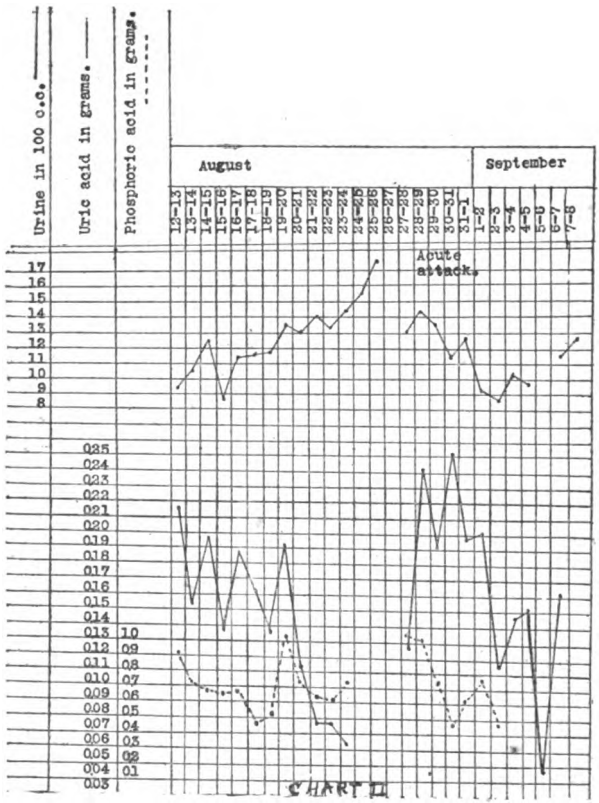
urine was placed on ice at once without waiting until after the 24-hour amount was collected makes the results in the second series of tests somewhat more accurate than those in the first.) A record was kept of the temperature, pulse, respiration, and number of stools. Frequent leukocyte counts were made. The 24-hour amount of the urine, the specific gravity, and the daily excretion of uric acid and phosphoric acid were estimated, the same methods being used as in the first series. A number of determinations of the total acidity of the urine was also made. Both the Freund and the Folin methods were used in parallel tests. The room temperature varied from 70° F. to 83° F.



During this series of tests the patient was kept on the following diet: Breakfast, an egg, soft boiled, with bread and butter and glass of milk. Dinner, same as breakfast. Supper, a bowl of bread and milk. The only modifications were: August 27, he ate no eggs; August 31, the egg was omitted at breakfast; September 1, breakfast consisted of a slice of bread and butter; September 2, no eggs were eaten. Water was allowed, but the patient drank little of it (except on August 28, when he drank six glasses); on August 30 and 31 he did not take any water.

With regard to exercise and bodily exertion, the patient walked about

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the ward and helped in light work, such as washing dishes and making beds.

He was quite free from pain until August 19, when one of the joints of the right forefinger became painfully swollen, and August 20, the skin ruptured, and a discharge of whitish puriform material occurred. He had little pain from that time until August 29. August 29, 6 a. m., the left heel became swollen and painful. August 30, patient in bed. The skin over the heel broke, and a profuse bloody discharge containing

TABLE II.

Date.	Urine in cc.	Specific gravity.	Uric acid in grams.	Phosphoric acid in grams.	Remarks.
August 12–13.	985	1015	0.216	0.908	No marked pains.
" 13–14.	1030	1010	0.154	0.715	
" 14–15.	1230	1010	0.196	0.682	
" 15–16.	890	1012	0.138	0.649	
" 16–17.	1140	1015	0.188	0.684	
" 17–18.	1180	1014	0.161	0.483	
" 18–19.	1190	1012	0.138	0.505	Joint of forefinger swollen.
" 19–20.	1350	1014	0.192	1.026	Discharge from forefinger.
" 20–21.	1300	1015	0.112	0.728	Comparatively free from pain.
" 21–22.	1400	1014	0.079	0.63	
" 22–23.	1320	1011	0.076	0.60	
" 23–24.	1420	1011	0.063	0.724	
" 24–25.	1550	.....	.....	.....	
" 25–26.	1750	.....	.....	.....	
" 26–27.	.....	.....	.....	.....	
" 27–28.	1300	1011	0.126	1.059	
" 28–29.	1420	1010	0.231	1.022	Left heel swollen; painful.
" 29–30.	1350	1011	0.192	0.735	Heel discharging freely.
" 30–31.	1150	1011	0.250	0.493	.....
September 1–2	1280	1011	0.196	0.62	Pain less marked.
" 2–3	930	1011	0.202	0.781	.....
" 3–4	1010	1012	0.111	0.484	No pains.
" 4–5	980	1012	0.147	.....	Patient out of bed.
" 5–6	.....	.....	0.152	.....	.....
" 6–7	1150	.....	0.046	.....	.....
" 7–8	1260	.....	0.160	.....	.....
" 8–9	1525	.....	.....	.....	.....

white particles occurred, which gave marked relief. At this time there was pain on swallowing, pain and soreness in the neck and about the clavicles, with more or less pain throughout the entire left side. Hot lead water and laudanum were applied the painful areas. At 5 p. m. the temperature was 100.2°. August 31, the pain and stiffness were much less marked. September 1, some headache and stiffness about the back of the neck. September 2, pains all over the body. September 3, pains had disappeared, and patient felt better. September 4, patient out of bed. No medicine was given during this series of tests.

Table II and Chart II give the amount of urine in 24 hours, the specific gravity, and daily excretion of uric acid and phosphoric acid.

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Table III—the temperature, pulse, respiration, stools, and leukocyte counts.
Table IV—the determinations of the total acidity of the urine.

Daily microscopic examinations of the urine showed constantly a trace of albumin, and a few hyaline and granular casts. Clinical urea determinations by the Doremus method gave low values—17 grams to 20 grams per day.

It will be noted from a study of the tables and charts that the *"endogenous"* uric acid elimination was, for the most part, below that of a normal individual. According to the investigations

TABLE III.

Date	Hour.	Temperature.	Pulse.	Respiration.	Stools.	Leukocytes.	
						Hour.	Number per cm.
August 12–13.	10.30 a.m.	98	72	24	0	.....	.....
" 13–14.	9.20 a.m.	97	80	25	0	.....	.....
" 14–15.	11.15 a.m.	97.2	80	16	1	11.15 a.m.	9,000
" 15–16.	10.15 a.m.	97.6	72	24	1	4.30 p.m.	7,000
" 16–17.	3.30 p.m.	97.6	72	20	1	3.30 p.m.	7,000
" 17–18.	9.30 a.m.	97.6	72	20	1	9.30 a.m.	6,000
" 18–19.	2.30 p.m.	97.8	80	18	1	.....	.....
" 19–20.	5.30 p.m.	98.8	68	30	1	5.30 p.m.	6,400
" 20–21.	2.30 p.m.	98	72	20	1	.....	.....
" 21–22.	3 p.m.	98.8	64	24	1	3 p.m.	5,200
" 22–23.	6.15 p.m.	98.4	68	20	1	6.15 p.m.	5,200
" 23–24.	3.15 p.m.	98.4	68	20	1	3.15 p.m.	6,440
" 24–25.	4 p.m.	98	72	18	1	.....	.....
" 25–26.	9 p.m.	99.6	72	18	1	.....	.....
" 26–27.	2.30 p.m.	98	64	20	1	2.30 p.m.	6,060
" 27–28.	8.30 a.m.	98	84	20	1	8.30 a.m.	6,000
" 28–29.	11 a.m.	98.8	84	20	1	11 a. m.	6,000
" 29–30.	9.30 a.m.	98	72	20	1	.....	.....
" 30–31.	5 p.m.	100.2	72	20	1	5 p.m.	7,000
" 31–1..	9.30 a.m.	98	72	20	1	.....	.....
September 1–2	11 a.m.	97	72	16	1	11 a.m.	7,000
" 3–4	9 a.m.	98	72	....	1	.....	.....
" 4–5	.....	99	80	18	1	.....	.....

quoted, the extremes in daily excretion in different normal individuals were 0.2 grams and 0.7 grams. In this case the daily excretion was always below 0.2 grams, except at the time of acute exacerbations, when the highest point reached was 0.27 grams. The lowest point reached was 0.046 grams. Between these two extremes were marked fluctuations. The values in the intervals between acute exacerbations were not invariably low, but on several occasions approached the highest values reached during an attack. Kaufmann and Mohr[9] found the endogenous uric acid excretion in five cases of chronic gout to be within

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normal limits, varying between 0.357 grams and 0.660 grams per day in different cases. One of Futcher's[10] patients, during three periods of twenty-four hours each, had practically no uric acid excretion.

In a general way in the first series, the phosphoric acid curve follows the uric acid curve, as closely, certainly, as in Cases II and III, reported by Futcher.[10] It will be noted, however, that in the second series of tests, between August 27 and 31, the phosphoric acid curve fell, while the uric acid curve was rising to

TABLE IV.—ACIDITY.

Date.	Cc. of uranium solution used for 50cc. urine.	Freund method.		Cc. of N/10 NaOH per 25 cc. urine.	Folin method.	
		Corresponding number of cc. of N/10 NaOH per 100 cc. urine.	Cc. of N/10 NaOH per 24 hours.		Cc. of N/10 NaOH per 100 cc. urine.	Cc. of N/10 NaOH per 24 hours.
August 17–18.	1.35	3.69	43.54	2.8	11.2	132.16
" 18–19.	1.2	3.27	38.91	2.9	11.6	138.04
" 19–20.	2.1	5.71	77.08	3.95	15.8	213.30
" 20–21.	1.2	3.27	42.51	5.87	23.58	307.54
" 21–22.	1.55	4.23	59.22	5.95	23.8	333.20
" 22–23.	1.2	3.27	43.16	5.1	20.4	269.28
" 23–24.	1.15	3.17	45.01	5.15	20.6	288.85
" 24–25.	.....	.....	.....	.....	.....	.....
" 25–26.	.....	.....	.....	.....	.....	.....
" 26–27.	.....	.....	.....	.....	.....	.....
" 27–28.	2.65	7.24	94.12	7.67	30.68	398.84
" 28–29.	2.5	6.83	96.98	6.6	26.4	374.88
" 29–30.	2	5.46	73.71	5.15	20.6	278.10
" 30–31.	1.2	3.27	37.60	4.85	19.4	223.10
" 31–1..	1	2.73	34.94	5.3	20.52	262.71
September 1–2	1.47	4.01	51.32	7.7	28.8	257.84
" 2–3	.....	.....	.....	.....	.....	.....

its highest point. This recalls Futcher's statement in regard to his Case III: "There was, however, an unexplainable drop in the phosphoric acid curve between April 8 and 17, when it failed to correspond at all with the uric acid curve." In the paper referred to there is no statement indicating that the patient was kept on a purin-free diet. It will be noted that the daily excretion of phosphoric acid in this case is considerably below the normal given by Futcher (2.5 grams); the highest point reached in our determinations being 1.57.

The leukocyte counts made at irregular intervals in connection with the second series of tests do not suggest any definite rela-

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tionship between the number of leukocytes and either the phosphoric acid or uric acid excretion. No constant digestive leukocytosis was noted, and the count was always distinctly within normal limits.

The total acidity was determined both by the Freund[11] method (which is based upon the assumption that the acid reaction of the urine is referable exclusively to the diacid phosphates) and by the Folin[12] method. Folin believes that the Freund and all similar methods are open to the fatal objection that a considerable part of the acidity of the urine is due to organic acids. He titrates the urine with decinormal sodium hydrate solution after first guarding against the disturbing effect of calcium and ammonium salts by the addition of about 20 grams of powdered potassium oxalate to the 25 cubic centimeters of urine titrated.

In this series of tests the Folin method gave uniformly higher values than the Freund method. Even the determinations by the Folin method were below the normal values given by Folin[13] as varying, in thirty normal urines, between 554 cubic centimeters and 669 cubic centimeters of decinormal sodium hydrate solution per twenty-four hours, and below values he obtained for individuals on a similar purin-free diet. The highest value obtained in this series was 398 and was found on August 28. It was nearly as high on August 29. These were the days when the patient was suffering more pain than usual. No constant relationship appears to exist between the total acidity and the excretion of uric acid in this case.

Definite conclusions regarding uric acid formation cannot be drawn from such experiments as are here reported. While it has been considered justifiable to make important deductions regarding uric acid formation in health from a study of uric acid excretion, the presence of disease conditions introduces disturbing factors. The recent work of Löwi,[14] Folin[15] and others, indicates that even the widely accepted theories of Burian and Schur regarding uric acid metabolism in health may not be well founded. Löwi claims that it is impossible by our present methods to determine accurately the amount of exogenous or endogenous purin eliminated. Folin[15] has found the endogenous uric acid elimination in health not to be constant on certain purin-free diets. He questions whether all the endogenous uric acid eliminated in health is derived from the nuclein of body cells. The possibility of the synthetic formation

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of endogenous uric acid in man, even in health, is asserted by several investigators.[16] If it were true, as has been claimed by Burian and Schur, that in health the uric acid eliminated in the urine represented half of that formed in the body, and this proportion remained constant in disease, quantitative uric acid determinations would certainly be of great value. Other factors in metabolism, such as digestion, sleep and exercise, would, however, still have to be considered. Digestion affects uric acid elimination decidedly, if constipation or diarrhea occur. According to Schittlhelm,[17] the purin bodies found in feces are in part derived from unabsorbed parts of the food, in part from bacteria, and in part from the secretion of intestinal glands. In diarrhea, a rapid passage of food purins through the intestine would increase the fecal output, and less purin would be absorbed to be excreted in the urine. In this case there was no diarrhea, the bowels moving regularly, as noted in Table III. Siven,[18] Pfeil and Rockwood have found the elimination of uric acid to be greater by day than by night; Rockwell suggests that the difference is due to a lessened rate of cellular metabolism during rest in bed. Sherman[19] has failed to find any increase in uric acid elimination resulting from vigorous exercise. Rockwood[18] found an increase in endogenous uric acid elimination after exhaustive labor, but not after moderate exercise. It has been maintained[20] that if the subject is in poor physical training, exercise causes an increase in uric acid elimination. It is probable that there was chronic nephritis in this case; this introduces another disturbing factor.

Whether there is really a constant relationship between the endogenous uric acid elimination and the "endogenous" phosphoric acid elimination in this case, cannot be inferred, since the diet, while purin-free, was not free from elements containing exogenous phosphoric acid. Phosphorous may be taken into the food in other forms than that contained in the nucleins, and according to Chalmers Watson [21] and others, this prevents any possible parallelism in the curves. Kauffmann and Mohr [22] state that phosphoric acid excretion varies with the varying needs of the body for phosphoric acid.

Horbaczewski's theory that endogenous uric acid was derived exclusively from the breaking down of leukocytes is no longer accepted. The work of Magnus-Levy,[23] Richter,[24] and others, has demonstrated the fallacies of his arguments and there does

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not now seem to be any reason why the leukocyte curves should parallel the uric acid curve. There is no constant parallelism between the two in this case.

SUMMARY.

The uric acid elimination in a case of chronic gout kept on a "purin-free" diet was below so-called normal limits. In the intervals between the exacerbations there was marked variation in the amount of uric acid eliminated. Low values were reached preceding acute symptoms, and at times during the intervals the excretion was very low, at other times, however, the highest values reached during an attack were approached.

The phosphoric acid elimination was below normal. In the first series of tests the phosphoric acid curve followed the uric acid curve quite closely; in the second series, not at all.

The leukocyte counts were normal. They did not vary with the uric acid excretion. No digestive leukocytosis was noted.

The acidity was at all times below the average normal acidity. The highest values were obtained during one of the acute exacerbations.

Present views regarding uric acid elimination may be summed up in a few words: The principal source of the uric acid eliminated by man under normal conditions is the nucleins. We find an increased elimination of uric acid following the ingestion of substances contained nucleins. This source of uric acid can be controlled. The endogenous uric acid is probably derived from more than one source. A large portion comes from the decomposition of the nuclein of body cells, but a part is probably formed by direct synthesis. When certain purin-free diets have been used, the endogenous uric acid has in certain individuals shown a somewhat constant value in health, when other factors in metabolism were constant. When other forms of purin-free diet were employed the amount of endogenous uric acid was not constant, even in health. In disease the elimination of uric acid has shown marked fluctuations. How large a portion of the endogenous uric acid elimination under pathologic conditions is formed by synthesis is not known. The nucleins are one source of the phosphoric acid excretion in the urine, but not the only source, and there is no constant relationship between uric acid and phosphoric acid excretion.

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Though the leukocytes are a source of endogenous uric acid they are by no means the only source, and their number has no constant relationship to the excretion of uric acid. The work of the past few years has shown the fallacies in certain generally accepted theories regarding the source of uric acid and established definitely a very few facts in regard to uric acid metabolism. The part which uric acid plays in gout is still unsettled.

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Reprinted from ALBANY MEDICAL ANNALS, January, 1906

MALIGNANT OVARIAN TUMORS IN CHILDREN; WITH REPORT OF A CASE.

BY J. LEWI DONHAUSER.

(From the Bender Laboratory, Albany, N. Y.)

The following case of a malignant ovarian cyst in a girl thirteen years old, emphasizes some of the clinical features of this unusual condition and on this account seems worthy of reporting in full.

History of the Case.

Miss C. P., a schoolgirl, aged 13, was admitted to the service of Dr. Willis G. Macdonald, at the Albany City Hospital, October 20, 1904, complaining of severe abdominal pain.

Family History.—Father, mother and two sisters living and well; two great aunts and one aunt and one uncle on father's side said to have had cancer.

Past History.—Very healthy child; no sickness before present illness; menstruated for the first time on September 3, 1904; flowed five days and menstruation was apparently normal. Leucorrhoea present during last few months.

Present Illness.—On the afternoon of September 11th, menstruation having ceased,she was taken with severe colicky pains in abdomen, which radiated into the shoulder. These pains soon disappeared and she became quiet until about 10 p. m., when she was again seized with an attack of a similar character. At the end of 24 hours she felt well, and remained so for three weeks, when she had a third attack similar to the previous ones. Since the onset of this last illness (on the 11th of October) she has been incapacitated, owing to the frequent and severe attacks of pain. For the past few days she has had fever (102° and over) and has been vomiting.

Clinical Diagnosis.—Ovarian cyst (ruptured) with twisted pedicle.

Operation.—A median incision exposed the peritoneum through which could be seen haemorrhagic material in the abdominal cavity. On opening the latter, it was seen to be filled with free and clotted blood. Further examination revealed an ovarian cyst which had ruptured. The blood was wiped out of the peritoneal cavity and after ligating the pedicle of the cyst, it was removed. A glass tube was inserted and the abdominal incision closed with silkworm gut. The patient was discharged November 12, 1904.

She was admitted to the service of Dr. Macdonald again on November 29, 1904, and gave the following history. About five days after the patient left the hospital she complained of soreness and pain in the right side which was soon followed by an attack of sharp pain lasting from one afternoon until the next morning. She has had numerous other attacks since, the pain extending chiefly down the right leg. Her appetite has been poor and vomiting has been more or less constant.

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Her bowels have moved three or four times daily; stools have been pencil shaped; no bloody stools noted. She has lost weight and is very anaemic. For the last three days the patient has been kept in bed, on a strict liquid diet. Temperature for the last two or three days has been at least as high as 100.7°. A swelling on the right side of the abdomen was noticed before coming to the hospital.

An exploratory operation was performed on the 29th of November. An incision was made over the tumor, which was situated on the right side just below the liver. On opening the abdominal cavity a bloody fluid, in which were found pieces of grayish tissue, escaped. The cavity was thoroughly irrigated and a drainage tube, flanked with strips of iodoform gauze, was inserted. The patient lived for nearly a month after the operation, but finally became delirious and restless, refused food, and died on December 20, 1904. An autopsy was made by Dr. E. MacD. Stanton, from whose notes the following descriptions have been taken.

Anatomical Diagnosis.—General sarcomatosis of abdominal cavity. Extreme secondary anaemia. Thrombus in right heart. Operation scars on abdomen.

Abdominal Cavity.—The entire left side of the abdomen and pelvis is filled by a tumor mass which reaches to the anterior abdominal wall and is for the most part covered by a portion of the omentum. The left border of this mass extends from a point 5 cm. to the left of the symphysis pubis upward to the under border of the liver at a point 5 cm. to right of the median line. The coils of intestine adjacent to the tumor mass are loosely adherent to one another by easily torn adhesions which are apparently, for the most part, composed of the tumor itself. The remainder of the abdominal cavity contains a few cubic centimetres of bloody fluid. The peritoneal surfaces show a slight loss of lustre, with here and there, small tumors adherent to the peritoneum. These smaller masses vary from a few millimetres to 4 or 5 centimetres in diameter. Their surfaces are smooth with a thin peritoneum-like covering. Two of these masses situated on the under surface of the diaphragm have caused corresponding depressions in the right lobe of the liver. The head of the caecum and appendix together with the pelvic organs are imbedded in the new growth. The ascending colon and small intestines have been pushed over the left border of the tumor.

The general structure of the large and smaller tumors is similar. The free surface of the larger tumor is somewhat lobulated and of a mottled grayish and dark red color. The cut surface of the firmer portions of the tumor is also mottled grayish yellow and dark red, the red areas representing areas of hemorrhage into a soft succulent, grayish-yellow tissue which in many places is necrotic. The entire center of the larger mass is occupied by an ill-defined area of softening which is filled with partially clotted blood and fragments of necrotic tumor tissue. The tumors do not infiltrate the tissue beneath the peritoneum, it being possible in the case of the larger tumor to strip the parietal peritoneum from the abdominal wall.

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Pelvic Organs.—All pelvic structures are imbedded in the soft tumor mass described above. The left tube and ovary, the body of the uterus, the rectum and the bladder are negative except for the presence of tumor metastases or implantations on their peritoneal surfaces. The right ovary is missing, together with all but the proximal 3.5 cm. of the right tube. On the stump of the right tube are seen several silk ligatures which show almost no evidence of encapsulation.

Liver.—Weight, 1560 grammes. The upper surface of the right lobe shows several depressions, the two larger of which measure respectively 2 and 5 cm. in diameter. These depressions are caused by two tumor masses which are adherent to the under surface of diaphragm. The under surface of the right lobe of the liver is in contact with a shaggy grayish-yellow blood stained mass representing the upper and of the large tumor mass described above. Adherent to the under surface of the left lobe of the liver is another tumor mass 2.5 cm. in diameter. On section the liver presents a pale brownish yellow surface with indistinct markings.

Gastro-intestinal Tract.—Appendix measures 15 cm. in length and is imbedded in the tumor mass. The remainder of the gastro-intestinal tract is negative, except for the presence of small new growths scattered here and there over its peritoneal surface.

Pleural cavities, pericardial cavity, heart, spleen, kidneys, adrenals, pancreas, vagina and external genitals and cavity of the uterus are all negative.

Gross and Microscopic Appearances.—The specimen removed at the first operation was described by Dr. Stanton as being a large, mutilated, haemorrhagic and necrotic ruptured unilocular ovarian cyst. Its surface was fairly smooth though in a few areas could be felt fine hard granules, and its lining membrane was covered with intimately adherent blood clots.

On microscopic examination isolated groups of cells suggesting cancer were found, but these were stained so poorly, owing to the necrosis of the cyst wall, that a positive diagnosis as to their character could not be made.

The tissue removed at the second operation, on November 27th, and examined by Dr. Stanton, consisted of a few fragments of blood stained material. The anatomical diagnosis was then made of "multiple malignant growths due to implantation from a ruptured ovarian cyst." Microscopic examination of these tissues showed a highly cellular stroma composed of numerous spindle and round cells of both the large and small type. These large spindle and round cells constituted the predominating cells of the stroma. Distributed here and there in this tissue were numerous masses of epithelial cells arranged in "irregular gland-like tubules." This cellular arrangement led to the microscopic diagnosis of "so-called adeno-sarcoma."

Sections of the tumor growth removed at autopsy show a highly vascular tissue, many of the blood vessels of which are definitely formed and distinctly show the three vascular coats. Here and there are large areas of necrosis and haemorrhage about which are strands of

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a well formed granulation tissue. The histologic picture is somewhat intricate, inasmuch as in different sections the character and arrangement of the cells vary. In all, however, a very noticeable element is the rambling stroma, in the meshes of which are various types of cells, some resembling the spindle and round cells of sarcoma, others distinctly epithelioid, and still others with syncytial arrangement and again cells of definite epithelial or endothelial type. The latter are often arranged in gland-like tubules.

Examination of the smaller peritoneal nodules reveals practically the same picture as that found in the main tumor mass, namely, a stroma of spindle and round cells with masses of epithelium arranged in gland-like fashion. One section, however, taken from a nodule attached to the peritoneum by a slight and slender pedicle, presents an interesting picture of a well formed cyst. The wall of this cyst is composed of masses of spindle cells arranged as in sarcoma while the cavity is lined by columnar epithelium. This section resembles closely the new growth known as cystic adeno-sarcoma.

From the histological picture of the main tumor growth as well as that of the smaller nodules, it is evident that a microscopical diagnosis is very difficult. Owing to the peculiar arrangement of the epithelium scattered throughout the growth, one is tempted to consider the tumor as an adeno-carcinoma. On the other hand, however, the appearance of the stroma, which seems to be an intermediary type between newly formed connective tissue and true ovarian stroma containing as it does a vast number of spindle and round cells almost entirely devoid of intercellular substance, suggests a sarcomatous growth. Indeed, many malignant growths of the ovary present such peculiarities in their structure that various terms have been applied to them in attempts to combine the sarcomatous, the carcinomatous and the cystic characteristics in a single name applicable to all. Thus we have the terms adeno-carcinoma, adeno-sarcoma, cystic adeno-sarcoma, cystic endothelioma, sarco-endothelioma and Leopold's endothelioma lymphaticum and endothelioma vascularis. Poupinal speaks of secondary tumors as being of the sarco-carcinomatous type, although he does not state that the primary growth also may be a mixed tumor. Echardt and Pomorski have used simply the term " endothelioma of the ovary."

When such a number of terms are applied to these mixed tumors, how are we to histologically differentiate between them, and are we always justified in allowing a diagnosis to rest on a few sections? Kelly points out that " a thorough sifting of material from ovarian tumors, in the pathological laboratory, has served to demonstrate the necessity of a careful microsocopical examination in every

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case;" and so an attempt has been made to examine most carefully the tumor which is here reported. The result, however, has been unsatisfactory and no definite conclusion has been reached. Adena-carcinoma or "adeno-sarcoma" seems to be the most plausible term to apply in this instance, but each has objections. We must be satisfied therefore in describing it, as a malignant ovarian tumor, the stroma of which resembles ovarian stroma and in places suggests a sarcomatous structure, while scattered throughout it are masses of cells having the arrangement of an adeno-carcinoma.

The history of this case brings out sharply the following points:

1 Ovarian cysts may occur in children and may be malignant.

2 The pedicle may become twisted and as a result give rise to severe abdominal pain, thus leading to a diagnosis of the cyst.

3 The rupture of the cyst and the distribution of its contents throughout the peritoneal cavity may lead to a general implantation of the growth and soon cause death.

4 The histological diagnosis of these cases is frequently difficult.

Little is said in either the text-books or the general literature concerning malignant ovarian growths in children. My interest in the case here reported has prompted me to examine the histories of the various cases heretofore reported in regard to the following points.

1 What are the principal malignant ovarian tumors in children?

2 What is the relative frequency of these tumors?

3 Do malignant ovarian tumors present any clinical manifestations different from those presented by the benign growths?

4 How frequently do accidental conditions such as twisting of the pedicle or rupture of the cyst give the first warning of the presence of an ovarian growth?

5 Are seemingly benign growths of the ovary to be looked upon as harmless, as are benign growths of other organs.

Unfortunately, I have not been able to obtain much information, for the references are few, and, in the majority of the cases, meagre in clinical data.

The cases of ovarian tumors which have been reported as occurring in children, embrace a number of types of new growths, which may conveniently be divided into the benign cysts, sarcoma and carcinoma; and in addition to these, a fourth type, the mixed tumor, which, owing to the difficulties attending

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the determination of its structure and histogenesis, affords scope for argument as to its classification.

The benign cysts may be divided into the dermoid, and the simple uni- and multilocular cysts. The sarcomata are usually of the round or spindle cell types; while the adeno-carcinoma seems to be the most prevalent type of the epithelial tumors. The mixed tumors have been discussed in the first part of this report.

It is impossible to arrive at conclusions regarding the benignancy or malignancy of new growths of the ovary reported in the literature as "cysts." The fact that they are thus reported does not in the least confirm the idea that all are benign. Our own case shows the possibilities of malignancy in an apparently simple cyst.

Upon careful review I have been able to collect seventy-two cases of malignant tumors occurring in girls between the ages of twenty-two months and fifteen years. The relative frequency of the malignant tumors as compared with the benign growths of the ovary in children is comparatively small. Whether this is due to the fact that histological study has been neglected in a number of cases, or whether perhaps, the very small areas of the cyst wall which contain the malignant cells have escaped the examiner's notice, or whether cases have been reported too soon after the operation, thus affording little time for the observance of recurrence or whether surgeons have failed to report cases which have ended fatally, it is not my purpose in this report to state although these various possibilities have occurred to me during this study of the literature.

The fact however remains that malignant tumors of the ovary do occur in young children, and it is therefore the duty of the physician and the surgeon to look upon all ovarian growths as possessing possibilities of malignancy.

A study of the reports of malignant ovarian tumors here collected reveals the fact that clinically it is impossible at first to distinguish the benign cyst or tumor from a malignant growth.

The symptoms of the two conditions may be identical and to this fact is due the difficulty of differentiating between the two forms. Both may develop slowly and without causing the patient pain, as the latter seldom is present unless a twist of the pedicle or some other complication occurs. As the tumor grows, however, symptoms referable to a malignant growth may follow,

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such as emaciation and those arising from metastasis or implantation. The histories present little variation since the health of the individual, in the majority of the cases, has been reported as "good" up to the third, fourth, fifth or sixth month before the detection of the new growth.

Symptoms calling attention to the tumor vary.

1 Some cases were discovered accidentally in operating on other organs.

2 In others, symptoms referable to an abdominal tumor, such as tightness of the clothing, dyspnoea, or constipation, have led to the diagnosis.

3 In some cases the patient came under observation on account of pain.

4 In a few cases the patient was examined on account of an associated bloody vaginal discharge.

5 Symptoms of an acute abdominal condition arising from twisting of the pedicle or rupture of the tumor, indicated the proper diagnosis in several instances.

In some of the cases here tabulated, the diagnosis of sarcoma of the kidney, hyatid of the liver, tuberculous peritonitis, sarcoma of the spine, hæmatocele, hydronephrosis or typhoid fever was made. An astonishingly small percentage of the diagnoses were correct, showing beyond a doubt that the condition when it does occur in children is not readily recognized owing either to the difficulty of interpreting the symptoms or to the infrequency of the disease.

The occurrence of malignant ovarian cysts in children and the impossibility of differentiating them from benign cysts before metastases or implantations occur emphasizes the importance of an early diagnosis and operation in all cases. The case reported in this article supports this statement as does also the experience of the following investigators. De Senety states that "it seems impossible to draw a line of demarcation between ovarian cysts and ovarian cancers;" Kelly says that "from a practical standpoint all ovarian tumors must be considered as malignant until removed and proved otherwise." Pozzi remarks that "it is much better to always take the worst view of the case and always to fear generalization." Hofmeier and Cohn have, too, layed much stress on the fact that "glandular cysts may present cancerous degeneration," and Leopold fearing this degeneration has given it as a general rule that every ovarian

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tumor should be removed as soon as it is recognized. Bland Sutton quotes Jessup who once reported a case in which a ruptured dermoid cyst metastasized to the liver, the suprarenal capsule and the mesenteric glands.

As regards the frequency of the disease at the different periods of early life, the cases which I have tabulated reveal the fact that 60 per cent. occur between the age of ten and fifteen, while the cases ranging from birth to five years form but about 14 per cent. of the total number.

Two tumors simply reported as malignant ovarian tumors have not been included in the tables given below nor are the four carcinomata reported in Keating's Encyclopædia of Diseases of Children (p. 739) since the records contains no reference to age.

Table I—Type of Tumor According to Age.*

	Birth to 5 yrs.	5-9 yrs. incl.	10-15 yrs. incl.	Per cent.
Carcinoma	1	6	19	40
Sarcoma	8	10	18	55.4
Endothelioma	0	1	2	4.6
	13.8%	26.2%	60%	

In the table below the result of the operation has purposely been omitted inasmuch as the majority of the reports did not state whether the patient died as the result of operation, or as the result of the occurrence of metastases; also in those given as recoveries it was impossible always to determine the length of time after operation.

Conclusions.

1 Malignant ovarian tumors may occur in children.

2 In the first stages of the disease the clinical symptoms of the benign and malignant tumors are identical.

3 The tumor may be discovered accidentally or from symptoms arising from a rupture of the cyst or a twisting of its pedicle, which may be the first evidence of the presence of an ovarian tumor.

4 Children of all ages are susceptible to the disease although it occurs most frequently in children between ten and fourteen years.

* The figures here given cannot be regarded as conclusive for in many cases no microscopic examination was made.

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5 All ovarian tumors should be regarded with suspicion because of the possibilities of malignancy.

6 Rupture of ovarian cyst should be guarded against because of the possibility of secondary implantations in the peritoneum.

7 Accurate classification of the mixed tumors is frequently impossible in the present state of our knowledge.

SUMMARY OF REPORTED CASES OF MALIGNANT OVARIAN TUMORS.

No.	Reporter	Age	Tumor	Reference
1	Brown, R.....	9mo	Carcinoma	See reference to case No. 35.
2	Harris,.....	22...	Endoth. Sarcoma...	Am Jour, Obst. 1904, L, 530.
3	Flatau.....	22mo	Sarcoma.....	Münch. Med. Wochenschr. 1903, 532.
4	Hoffman and Keyser	33mo	Cystic sarcoma.....	Am. Jour. Obst., 1897, XXXVI, 331.
		yrs.		
5	Evers.....	2½..	Sarcoma.....	St. Louis Courier of Med. 1884.
6	Gibb.....	2½..	Myxo-chondro sarcoma.....	Glasgow Med. Jour. 1903, LX. 100.
7	Cameron.....	3½..	Sarcoma.....	Glasgow Med. Jour. 1889 (4) S XXXI, 37–40.
8	Foerste.....	4½..	Sarcoma.....	Am. Jour. Obst. 1896, XXXIII, 80.
9	Byford.....	4½..	Sarcoma.....	Chicago Med. Record 1891, II, 434.
10	Wiel.....	5 ..	Carcinoma.....	Johns Hopkins Hosp. Bulletin, 1905, XVI, 102.
11	Viering.....	5 ..	Sarcoma.....	See reference to case No. 31.
12	Page.....	6 ..	Sarcoma.....	Lancet, 1895, II, 1622.
13	Turner.....	6 ..	Sarcoma.....	See reference to case No. 31.
14	Cohn.....	6 ..	Sarcoma.....	Ditto.
15	Croom.....	7 ..	Sarcoma.....	Edin. Med. Jour. 1892–3, XXXVIII, 689.
16	Lucas.....	7 ..	Sarcoma.....	Presse, Med. 2 Mai, 1888.
17	Amann, Jr.....	7 ..	Endoth. Lymphaticum.....	Arch. f. Gynäk, XLVI, 493.
18	Gussenbauer.....	8 ..	Carcinoma.....	Wiener Med. Wochenschr. 1894, 47.
19	Stolypinski.....	8 ..	Sarcoma.....	See reference to case No. 31.
20	Chenoureth.....	8 ..	Carcinoma.....	Ditto.
21	Leopold.....	8 ..	Cystic Sarc.....	Arch. für Gyn. VI, 189.
22	Olshausen	8 ..	Carcinoma.....	See reference to case No. 31.

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No.	Reporter	Age	Tumor	Reference
23	Malius	9 yrs	Cystic sarc.	Lancet, 1890, I, 1174.
24	Forbes	9 ..	Myxo-sarc.	Australian Med. Jour., 1894, XVI.
25	Tanner, J. H.	9 ..	Carcinoma	See reference to case No. 35.
26	Leopold	9 ..	Carcinoma	See reference to case No. 31.
27	McBurney	10 ..	Sarcoma	Annals of Surgery, 1895, XXI.
28	Emmett	10 ..	Malignant tumor	Am. Jour. Obst. July 1881, XIV, 674.
29	Wagner	10 ..	Sarcoma	Arch. für Klin. Chir. XXX, 504.
30	Klebs	10 ..	Carcinoma	See reference to case No. 35.
31	Hubert	11 ..	Endothelioma Lymphaticum	Ueber Ovarial Geschwülste bei Kindern, Giessen, 1901.
32	Halliday Croom	11 ..	Sarcoma	Obst. Trans. Edin. XIV.
33	Leopold	11 ..	Carcinoma	See reference to case No. 31.
34	Olshausen	11 ..	Carcinoma	See reference to case No. 31.
35	Kluge	11 ..	Sarcoma	Dissertation, Marburg, 1894.
36	Kelly	12 ..	Sarcoma	Keating's Encyclop. of Diseases of Children, 730.
37	Olshausen	12 ..	Carcinoma	See reference to case No. 31.
38	Wagner	13 ..	Sarcoma	Arch. für Klin. Chir. XXX, 505.
39	Wells	13 ..	Sarcoma	Diseases of Ovaries, N. Y. 1873, 56.
40	Martin	13 ..	Carcinoma	Krankheiten der Eierstöcke, 1899, 369.
41	Leopold	13 ..	Carcinoma	Gyn. Ges. Dresden, 12 Juli, 1894.
42	Leopold	13 ..	Sarcoma	Ditto.
43	Eckhardt	13 ..	Sarcoma	Deutsche Med. Wochenschr., 1895, Vereins Beilage, 14.
44	Demakis	13 ..	Carcinoma	Dissertation Göttingen, 1895.
45	Flaischlen	13 ..	Carcinoma	See reference to case No. 31.
46	Cohn	13 ..	Carcinoma	Ditto.
47	Mertens	13 ..	Sarcoma	Deutsche Med. Wochenschr., 1894, 96.
48	Bode	13 ..	Sarcoma	Gyn. Geselsch. Dresden. 12 July. 1894.
49	Schrooder	13 ..	Carcinoma	Zeitschr. für Geb. und Gyn. 1883, 9369.
50	Smith	14 ..	Sarcoma	Lancet, 1874, vol. II.
51	Leopold	14 ..	Sarcoma	Arch. für Gyn. VI.

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No.	Reporter	Age	Tumor	Reference
52	Solger	14 yrs	Carcinoma	Beitrage zur Geburtshülfe und Gynäk, I, pg. 90.
53	Kaltenbach	14 ..	Carcinoma	See reference to case No. 31.
54	Muratoff	14 ..	Sarcoma	See reference to case No. 31.
55	Vonnegut	14 ..	Sarcoma	Dissertation, München, 1896.
56	Amann, Jr	14 ..	Endoth. Lympaticum	Gesellch. f. Geb. u. Gynäk zu München, 21 Jan. 1897.
57	Thornton	15 ..	Carcinoma	Med. Times & Gazette, London, 1883.
58	Dyonsten and Szabo.	15 ..	Carcinoma	Arch. für Gyn. XXXII. 194.
59	Koeberle	15 ..	Carcinoma	Gaz. Med. de Strassburg, 1875.
60	Geyer	15 ..	Carcinoma	Dissertation, Würzburg, 1897.
61	Bergesio, L	15 ..	Cysto-sarcoma	Osservatore Toreno, 1883, p. 529.
62	Hanks	15 ..	Cystic Carcinomatous Degeneration	Am. Jour. Obst., 1891, XXIV, 941.
63	Dembo	15 ..	Cystic Carcinamatous Degeneration	Dissertation, Berne, 1892,
64	Kratzenstein	15 ..	Sarcoma	Zeitschr. f. Geb. u. Gyn., XXXVI, 93.
65	Pick	15 ..	Sarcoma	Centralbl. für Gynäk 1894, 941.
66	Shatz	15 ..	Carcinoma	Corresp. Blatt. des Allg. Mecklenburg, Aerzte Vereins No. 106.

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Reprinted from ALBANY MEDICAL ANNALS, November, 1905.

ACTINOMYCOSIS LIMITED TO THE URINARY TRACT.

BY E. MACD. STANTON, M. D.,

(From the Bender Laboratory, Albany, N. Y.)

Actinomycosis limited to the urinary tract is of exceedingly rare occurrence. In a careful search of the available literature on human actinomycosis, an instance of such localization has not been found. It seems advisable therefore to record a case in which an actinomycotic lesion was limited to the kidney and bladder.

Actinomycosis involving the kidney as an incidental lesion in the pyæmic form of the disease is by no means uncommon; cases of this type having been reported by Ruhrah,[1] Mallory,[2] Kobler[3] and others. Both the kidney and bladder may be involved by the direct extension of lesions originating in other organs, the most frequent source being the gastro-intestinal tract. Such cases have been reported by Billroth,[4] Bell[5] and others.

The case here reported was clinically one of cystitis and pyelonephritis. The actinomycotic character of the kidney lesion was not recognized during life or at the time of the autopsy; but was discovered only upon histological examination of the kidney. For this reason it has been impossible to definitely determine certain points which might have an important bearing on the unusual localization of the lesions.

REPORT OF CASE.

(*Records of the Bender Laboratory, Autopsy No. 839.*)

Clinical history. Mr. W., white, aged 53, shoemaker, admitted to St. Peter's Hospital, January 7, 1905, service of Dr. Henry Hun.

Family history. Negative.

Personal history. Always healthy. Uses alcohol to excess. Denies venereal history.

Present illness. About two months before admission to the hospital the patient began to have difficulty in passing his urine. He could pass only a small amount at one time and the stream was small. For some time before admission he had been troubled with dribbling of urine over which he had no control. The passage of urine caused a burning sensation.

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Physical examination. Patient well developed. Pupils unequal, the left being irregularly dilated. Tongue enlarged, flabby, has fine tremor and is covered with white fur. Lungs resonant. Expiratory murmur prolonged. Heart sounds rather faint but otherwise normal. Abdominal examination negative. Bladder somewhat distended. Knee jerks present.

Urinary examination. January 8th, specific gravity 1020; acid; cloudy; trace of albumen; no sugar; many leucocytes and epithelial cells. January 23rd, specific gravity 1010; acid; cloudy; many pus cells.

Blood examination. January 23rd, haemoglobin 45 per cent.; leucocytes 6000.

Sputum examination. Many encapsulated diplococci. No tubercle bacilli found.

While in the hospital the patient ran an irregular temperature ranging from 99 to 103 and was slightly irrational the greater part of the time. In addition to the bladder symptoms he had a slight cough.

The treatment was purely symptomatic and consisted of cystogen in five grain doses every four hours together with a cough mixture, bismuth subnitrate, tannigenfi, strychnine and digitalis.

Autopsy. Made by Dr. Stanton eighteen hours after death.

The body is that of a large framed, poorly nourished adult male. Length of body 167 centimeters. Rigor mortis present. No œdema. Pupils unequal. Skin of a uniform yellow color except for moderate reddish discoloration of dependent parts. On the outer aspect of the right thigh 6 centimeters below the crest of ilium is an irregular, depressed reddish scar.

Abdominal cavity. No free fluid. Serous surfaces smooth and glistening. The omentum covers the intestines, is rich in fat and adherent by fibrous adhesions to the left side of the urinary bladder. The appendix points downward and its tip is adherent to the bladder. The transverse colon is adherent to the gall-bladder by a few fibrous bands.

Pericardial cavity. Negative.

Pleural cavities. Negative except for a few fibrous adhesions at both apices and at base of left lung.

Heart. Normal in size; pericardium and endocardium normal. Valves negative except for slight thickening at attached borders of aortic valves. The myocardium is firm and brownish red in color. Wall of left ventricle averages 14 to 16 millimeters in thickness.

Right lung. Surface smooth. On section numerous yellowish caseous nodules 1 to 5 millimeters in diameter are found at the apex, while in the middle lobe are many closely arranged recent tubercles 2 to 4 millimeters in diameter. These have a distinctly peribronchial arrangement. The lower lobe contains many similar nodules. Lung otherwise negative except for moderate carbon pigmentation.

Left lung. Pleural surface smooth except at apex and along posterior surface where there are a few fibrous tags. The apex is puckered containing a distinctly encapsulated caseous nodule 1 centimeter in diameter surrounded by a number of small firm nodules. Scattered throughout the remainder of the lung are nodules similar to those in the right lung.

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Spleen. Weight 240 grammes; capsule smooth; cut surface dark red in color; trabeculæ distinct; follicles indistinct.

Liver. Weight 1500 grammes. The capsule is normal except for a few thickened slightly wrinkled areas on the upper anterior surface of the lower lobe. On section the cut surface shows red and greyish yellow mottling; the darker areas correspond to the centres of the lobules. Gall-bladder and ducts normal.

Gastro-intestinal tract. The stomach is dilated; its mucosa smooth, pale and covered with a thick tenacious mucus. The remainder of the gastro-intestinal tract is negative except for a small pit-like depression in the middle of the transverse colon which represents apparently a healed ulcer.

Right Kidney. Weight 230 grammes. The capsule strips with some difficulty leaving an exceedingly pale greyish-yellow cortex with deeply injected stellate veins. On section the pelvis is filled with a thin greyish yellow purulent fluid. The pyramids and adjacent cortex are streaked by greyish yellow lines of purulent infiltration. In many places the areas of suppuration are confluent, forming abscesses 0.5 to 1 centimeter in diameter filled with a thick pus containing fragments of necrotic tissue. The ureter contains a thin cloudly fluid.

Left kidney. Weight 160 grammes. The capsule strips with some difficulty leaving a coarsely lobulated pale yellow surface. On section the cortex is seen to be markedly thinned. The cut surface is pale yellow in color and has a glistening appearance. The iodine test for amyloid is negative. Ureter normal.

Urinary bladder. The wall is very greatly thickened and is firmly bound to the pelvis on the right, posteriorly, by dense connective tissue containing islands of fatty tissue. On removing bladder numerous pus cavities are opened, a thick yellow pus escaping. The mucosa of the bladder which shows irregular losses of substance is slightly granular and has a mottled greyish yellow color. The cavity of the bladder is filled with a thick mucoid pus and many of the pus-containing pockets opened in removing the bladder are found to communicate with the bladder being, apparently, diverticula.

Prostate, seminal vesicles and *testicles.* Normal.

Adrenals. Normal.

Aorta. Normal.

Anatomical diagnosis. Chronic ulcerative cystitis. Suppuration in diverticula of bladder. Chronic pericystitis. Pyelo-nephritis (right). Chronic diffuse nephritis. Pulmonary tuberculosis. Fatty liver with slight chronic passive congestion. Scar of right hip. Scar of old ulcer (?) in colon. Chronic peritonitis. Chronic pleuritis.

Bacteriology. Cultures from right kidney sterile after 48 hours.

Histologic examination—Lung. Sections through nodular masses show tubercles made up of epithelioid cells, giant cells and lymphocytes and with central areas of caseation in and about which are slender beaded bacilli which stain by the Gabbet and Gram-Weigert methods. Careful examination of many sections revealed no evidence of the presence of actinomyces or other streptothricial forms.

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Left kidney. A few small focal areas in cortex show increase of interstitial tissue with an occasional hyaline glomerulus. Other glomerular tufts in these areas are shrunken and lobulated with wide intra-capsular spaces. The cells of the convoluted tubules are swollen and granular. A few hyaline casts are seen in the straight tubules.

Right kidney. Same chronic changes as in left kidney. In addition sections taken through the abscesses in the pyramids and cortex show irregular areas of suppuration. These areas are composed of polynuclear leucocytes and cell detritus in the midst of which are seen numerous typical actinomyces colonies with well developed "clubs." The persisting kidney tissues about such areas are diffusely infiltrated with lymphocytes, plasma cells and polynuclear leucocytes, while surrounding some of the larger abscesses there is a poorly defined zone of highly cellular newly-formed fibrous tissue. In the diffusely infiltrated areas the glomeruli and a large proportion of the tubules can still be made out. The mucosa and submucous tissues of the pelvis are infiltrated with lymphocytes, plasma cells and fibroblasts. A variety of staining methods, including those for the tubercle bacillus, prove the actinomyces to be the only organism present.

Bladder. Sections through the ulcerated portions of the bladder wall show an entire absence of epithelium. The mucosa is replaced by granulation tissue which is exceedingly rich in spindle shaped cells. On the surface of this tissue is a layer of partially necrotic cellular material containing a moderate number of leucocytes together with large clumps of cocci and a few bacilli. Small areas of necrosis extend into the deeper tissues of the bladder wall. The muscular coat shows a very marked increase of connective tissue of a highly cellular type. Although sections cut from a large number of blocks representing various portions of the bladder wall were examined for actinomyces neither colonies nor filaments could be found. Stains for tubercle bacilli are also negative.

Histologic diagnosis. Actinomycosis of right kidney. Chronic ulcerative cystitis with extensive formation of granulation tissue. Slight chronic diffuse nephritis. Pulmonary tuberculosis. Old blood pigment in spleen. Congestion and fatty metamorphosis of liver.

The presence of colonies of actinomyces in the kidney abscesses leaves no doubt as to the nature of the renal lesion. The failure to find either colonies or filaments of actinomyces in the bladder wall, however, raises a question concerning the character of the bladder lesion. On the other hand the presence of actinomycosis of the kidney and the peculiar character of the histological changes in the bladder wall indicate the probability that this lesion also is actinomycotic in nature.

The mode of infection in this case is doubtful and it is more than possible that the lesion in the urinary tract was secondary to a primary focus which had existed in some other part of the body but which had disappeared at the time of autopsy. The small scar-like area in the colon, the various peritoneal

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adhesions and the old scar on the outer aspect of the right thigh each suggest antecedent inflammatory conditions offering possible routes of infection; but no connection could be traced between any of these and the lesion in the urinary tract. The presence of tubercle bacilli in the lung and the absence of actinomyces dispose of any possibility that the lung lesion might have been the portal of infection.

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Reprinted from ALBANY MEDICAL ANNALS, January, 1906.

BENDER HYGIENIC LABORATORY.

Annual Report of the Director, for the Year Ending August 31, 1905.

BY RICHARD M. PEARCE, M. D.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1905.

The Work of the Laboratory. This may be conveniently divided into routine examinations, under-graduate teaching, instruction to special students and original investigation.

The nature of the routine work of the laboratory is shown in the accompanying table which gives the source of the material and the number and character of the examinations. Mr. Wachter's tabulation of his chemical and bacteriological examinations, made at the filtration plant, have been included in his annual statement to the Water Bureau of the City of Albany and do not appear in this report.

TABULATION OF THE ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1904, TO AUGUST 31, 1905.

	State Dept. of Health.	City Board of Health.	Albany Hospital.	St. Peter's Hospital.	Ellis Hospital, Schenectady.	Child's Hospital and St. Margaret's House.	Albany Orphan Asylum.	Coroner's Physicians.	All other sources.	
Autopsies	.....	.....	30	3	3	21	4	28	40	129
Surgical specimens	.....	.....	945	184	61	5	1	.....	75	1,271
Throat cultures	888	407	.....	.....	.....	.....	.....	.....	.....	1,295
Sputum	458	45	1	.....	.....	1	.....	.....	30	535
Widals	143	.....	86	17	.....	2	1	.....	39	288
Water, milk and ice	376	.....	.....	.....	.....	.....	.....	.....	32	408
Miscellaneous	7	.....	65	11	.....	5	1	.....	68	157
	1,872	452	1,127	215	64	34	7	28	284	4,083

These figures show a very satisfactory increase in the work in pathology, but a slight decrease in the number of bacteriological examinations. There is, however, an increase over last year of three per cent. in the total number of examinations. The greatest increase has been in the number of surgical specimens,

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which show an increase of 26.7 per cent. over last year. This is largely due to the fact that the laboratory now does the work of the St. Peter's Hospital, of Albany, and the Ellis Hospital, of Schenectady.

The laboratory courses during the past year (term of seven and a half months) to undergraduates of the Albany Medical School were as follows:

Pathology and bacteriology.—Drs. Pearce, Stanton, Winne and Sibley, eight and a half hours a week.

Normal histology.—Drs. Stanton and Boyd, six hours a week.

Clinical microscopy.—Drs. Laird and Sibley, two and a half hours a week.

Surgical pathology.—Drs. Elting and Carey, two and a half hours a week.

Histology and pathology, in connection with the course in obstetrics.—Drs. Lipes and Boyd, two and a half hours a week.

Anatomy and pathology of the nervous system.—Drs. Stanton and Boyd, one and a half hours a week.

In connection with the course in pathology the most serious need is some arrangement by which post-mortem examinations may be made before the entire class. At present, this instruction can be given only to small sections at irregular intervals. It would appear possible, by combined action of the Albany Hospital, the faculty of the Albany Medical College and the trustees of the Bender Laboratory, to arrange for proper facilities at the Albany Hospital. I respectfully suggest to the trustees the necessity of immediate action upon this question.

Physicians who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are Dr. R. Fletcher Van Heusen of San Francisco, Dr. Ellice McDonald of New York, Dr. C. G. McMullen and Dr. W. P. Faust of Schenectady, and Drs. J. A. Cox, J. A. Lanahan, J. A. Sampson, J. F. Rooney, A. J. Douglas, A. T. Hull and K. D. Blackfan of Albany. Undergraduates having similar privileges were Messrs. J. L. Donnhauser, Erastus Corning, Jerome Myers, E. W. Jackson, J. H. Linden, J. F. Robinson, S. P. Brush, R. A. Lawrence and F. C. Conway, students of the Albany Medical School, and Mr. Nelson Fromm, of Dartmouth Medical College. These gentlemen have assisted in the routine work of the laboratory, pursued special lines of study or engaged in research work.

Investigations completed during the past year are as follows:

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1. STANTON, E. MacD., The Sequence of the Pathologic Changes in Appendicitis.—*Journal of the American Medical Association, 1905, xliv, 1849.*

2. BALDAUF, LEON K., Cancer of the Appendix Vermiformis, with Report of Three Cases.—ALBANY MEDICAL ANNALS (*in press*).

3. CORNING, E., Retention Cyst and Diverticulum of the Appendix Vermiformis.—ALBANY MEDICAL ANNALS (*in press*).

4. LAIRD, A. T., The Elimination of Endogenous Uric Acid in Cases of Chronic Gout.—*American Medicine, 1905, x, 315;* ALBANY MEDICAL ANNALS, xxvi, 742.

5. PEARCE, R. M., Experimental Cirrhosis of the Liver.—*Journal of Experimental Medicine (in press).*

6. PEARCE, R. M., and STANTON, E. McD., Experimental Arteriosclerosis.—*Journal of Experimental Medicine (in press).*

7. STANTON, E. McD., Actinomycosis Limited to the Urinary Tract.—ALBANY MEDICAL ANNALS, xxvi, 738.

8. DONHAUSER, J. L., Malignant Ovarian Tumors in Children with Report of a Case.—ALBANY MEDICAL ANNALS (*in press*).

9. McDONALD, E., The Various Forms of Puerperal Sepsis with Report of Cases.—*American Medicine (in press).*

Other investigations not yet completed are:

A Study of the Effect of Haemolytic Sera upon the Blood and Blood-forming Organs by Dr. C. K. WINNE, Jr; A Study of the Action of Toluylendiamin upon the Blood and Blood-forming Organs by Mr. J. L. DONHAUSER; and a Study of Sarcoma of the Uterus by Dr. ELLICE McDONALD.

The expense of the experimental work has been defrayed by a grant from the Rockefeller Institute for Medical Research; a similar grant has been obtained for the ensuing year.

LABORATORY CLUB. During the past year an organization known as the Laboratory Review Club has been formed. This includes the regular staff and all instructors giving courses in the laboratory. Its object is to cover, in the form of general reviews, a few of the important lines of work in scientific medicine. These reviews are afterwards published in the ALBANY MEDICAL ANNALS. Physicians and students doing special work in the laboratory are invited to attend these meetings so that an average attendance of twelve to fifteen has been the rule. This club has been so enthusiastically supported

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by all members and its advantages are so evident that it will be made a permanent organization.

CHANGES IN THE STAFF. Dr. E. MacD. Stanton and Dr. Chas. K. Winne, Jr., who were reappointed as regular assistants, and Dr. E. F. Sibley, who volunteered as assistant without salary for one year, have constituted the laboratory staff for the past twelve months. To the conscientious and earnest efforts of these gentlemen is due in large part the present efficiency of the laboratory in all lines of work. To Dr. Sibley we are especially indebted for time and labor given without substantial recompense. Dr. Stanton, having received an appointment at the St. Mary Hospital of Chicago, resigned in June. Dr. Leon Kahn Baldauf (Johns Hopkins University, A. B., 1901; M. D., 1905) has been appointed his successor. Dr. Winne resigned September 1st to enter private practice in Albany and in his stead Dr. Kenneth D. Blackfan (Albany Medical College, M. D., 1905) has been appointed. On September 1st, Dr. Sibley also terminated his connection with the laboratory in order to become an assistant to Dr. A. W. Elting.

The great increase in all departments of our work has led to the creation of three new positions. The first of these, an assistantship in Neuro-Pathology, was made possible through the generosity of Dr. Henry Hun. To this position has been appointed Dr. La Salle Archambault (Albany Medical College, M. D., 1902), who enters upon his duties after two years special study of neurology in the laboratories and clinics of Europe. The second position, that of assistant in Surgical Pathology, is the result of the generous cooperation of Drs. Albert Vander Veer and Willis G. Macdonald. To this position has been appointed Dr. Harold Eugene Robertson (Carlton College, A. B., 1899; University of Pennsylvania, M. D., 1905).

The third new position, that of Pathological House Officer to the Albany Hospital, is the natural result of the great increase in laboratory work of the latter institution. Although the incumbent of the position is appointed by the Board of Governors of the Albany Hospital at the recommendation of its staff, and is therefore an officer of the hospital, it appears justifiable, as the greater part of his work will be in the Bender Laboratory, to consider him as an assistant in the latter institution. Dr. William M. Dwyer (Albany Medical College, M. D., 1905) has been appointed by the Board of Governors of the hospital to fill this position during the year ending June 1, 1906.

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The influence which these changes will have upon the work of the laboratory cannot be estimated. The staff for the past two years has been quite inadequate. The great variety and amount of our routine work including as it does, teaching, examinations for state and city boards of health, the autopsy work and the examinations of the surgical material of the various hospitals of this vicinity and the prosecution of special investigations has taxed the staff to its utmost and not infrequently has caused considerable embarrassment. Such difficulties, however, will be avoided by this increase in the staff.

Through financial assistance afforded by the Albany Medical College, the janitor service has been increased and this very important service is now highly satisfactory.

Mr. Leonard M. Wachter was reappointed for the year 1905-'06 as assistant chemist and bacteriologist, in charge of the Albany filtration plant.

IMPROVEMENTS, REPAIRS, ETC. These have been entirely practical and are not of great importance. The small room off the large class room has been transformed into a museum. Here has been formed the nucleus of a museum of gross pathology. On the first floor new quarters have been built and furnished for the janitor. Speaking tubes and call bells have been installed, thus obviating much unnecessary confusion and expediting the work. A set of framed bacteriological plates have been placed in the class room. During the past summer the usual amount of repairing, painting and varnishing of woodwork has been done. The building is in excellent condition and I have now nothing to suggest in the way of repairs or improvements.

Of great advantage has been the space regained by the removal of the State Antitoxin Laboratory. Of the four rooms thus vacated two are now devoted to general laboratory purposes, one has been fitted up as an operating room and the fourth has been reserved for Dr. H. C. Jackson, recently appointed Adjunct Professor of Physiological Chemistry in the Albany Medical School. Although Dr. Jackson's classes will be held in the new laboratory at the Medical School buildings, it seems advisable, owing to the many advantages offered by the Bender Laboratory and also on account of the proximity to the city and county hospitals, that space and facilities for research work be given him in this laboratory.

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STUDIES

FROM

THE BENDER

HYGIENIC LABORATORY

ALBANY, N. Y.

REPRINTS

VOLUME III

1906

FORT ORANGE PRESS
BRANDOW PRINTING COMPANY
ALBANY, N. Y.

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NOTE

THIS volume comprises the publications of the Bender Hygienic Laboratory based on the work for the year ending August 3, 1906. Some of these have appeared in other medical journals, but for the sake of uniformity all have been reprinted from the Bender Laboratory Number (January, 1907) of the ALBANY MEDICAL ANNALS. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *December*, 1906.

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STUDIES

FROM

THE BENDER

Hygienic Laboratory

ALBANY, N. Y.

REPRINTS

Volume III

1906

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Staff

(For the year ending August 31, 1906)

RICHARD M. PEARCE, M. D., *Director*

HOLMES C. JACKSON, Ph. D., *Physiological Chemistry*

LEON K. BALDAUF, M. D., *Pathology*

KENNETH D. BLACKFAN, M. D., *Bacteriology*

LA SALLE ARCHAMBAULT, M. D., *Neuro-Pathology*

H. E. ROBERTSON, M. D., *Surgical Pathology*
(Resigned May 1, 1906)

J. FLETCHER ROBINSON, M. D., *Surgical Pathology*
(Appointed June 1, 1906)

Pathological House-Officer

(Appointed by the Trustees of the Albany Hospital)

WILLIAM M. DWYER, M. D. (to February 1, 1906—resigned)

FRANK GEORGE SCHAIBLE, M. D. (February 1 to June 1, 1906)

C. W. LOUIS HACKER, M. D. (from June 1, 1906—)

Assistant Chemist and Bacteriologist

(In charge of the Albany Filtration Plant)

LEONARD M. WACHTER

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Laboratory Courses of the Albany Medical College

(Given in the Bender Hygienic Laboratory)

Session of 1905-'06

Pathology and Bacteriology

RICHARD M. PEARCE, M. D., *Professor of Pathology and Bacteriology*

CHARLES K. WINNE, JR., M. D., *Instructor in Bacteriology*

KENNETH D. BLACKFAN, M. D., *Instructor in Pathology and Bacteriology*

H. E. ROBERTSON, M. D., *Instructor in Pathology and Bacteriology*

Histology

LEON K. BALDAUF, M. D., *Instructor in Histology*

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Surgical Pathology

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Clinical Microscopy

ARTHUR T. LAIRD, M. D., *Lecturer in Clinical Microscopy*

E. V. FREDERICK, M. D., *Instructor in Clinical Microscopy*

Anatomy and Pathology of the Nervous System

LA SALLE ARCHAMBAULT, M. D., *Instructor in Neurology*

Antitoxins and Immunity

HERBERT D. PEASE, M. D., *Lecturer upon Antitoxins and Immunity*

Anatomy and Pathology of Obstetrics

H. JUDSON LIPES, M. D., *Clinical Professor of Obstetrics*

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CONCERNING THE PRODUCTION OF CYTOTOXIC SERA BY THE INJECTION OF NUCLEOPROTEIDS.*

By RICHARD M. PEARCE, M. D.,
Professor of Pathology and Bacteriology,
AND
HOLMES C. JACKSON, Ph. D.,
Adjunct Professor of Physiological Chemistry, Albany Medical College.
(*From the Bender Laboratory, Albany, N. Y.*)

This investigation was incited by the publication of Beebe's studies[1] which describe the production of specific cytotoxic sera for the liver, kidney and pancreas as the result of treating animals with the respective nucleoproteids of these organs. As one of us[2] had previously made a somewhat extensive study of cytotoxic sera prepared by the injection of various somatic cells, and had reached conclusions which did not justify the views then current concerning the specificity of these bodies, it seemed advisable, in view of Beebe's very definite results, to further pursue these studies.

The Development of Our Knowledge of the Cytotoxins.

It may not be out of place to interpolate here a few words concerning the very definite change in opinion which has occurred during the past few years concerning the specificity of the cytotoxins. Shortly after the early publications of Ehrlich and his associates concerning the production of immune hemolysin, a vast number of publications describing specific sera for practically all cells of the body appeared in rapid succession. In most of these studies an attempt was made to demonstrate a specificity according to morphological rather than receptorial affinity in disregard of the very clear and definite statement of Ehrlich and Morgenroth. Those who denied a morphological specificity based their opinion on the observation that by the injection of cells, as those of the testicle, apparently free from blood, there resulted not only an antiserum for these cells, but also an hemolysin. This was explained by those who believed in morphological specificity by assuming that a number of red blood corpuscles, sufficient to produce a hemolysin, had been injected with the semen. Later, however, the production by a large number of investigators of hemolysin by the injection of fluids entirely free from red corpuscles, as serum and urine, demonstrated the production of antibodies from free

* Conducted under a grant from the Rockefeller Institute for Medical Research. Read before the Section in Pathology of the British Medical Association, Toronto, August 21 1906. Published also in *Jour. Infect. Dis.*, 1906 iii, 742.

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receptors and firmly established Morgenroth's contention that specificity is a matter, not of cells, but of receptors. Despite these very conclusive demonstrations later investigators, who attempted to produce antisera for the cells of various organs, continued to use emulsions of unwashed organs in utter disregard of the presence of free receptors in the organ juices and also without consideration of the antibodies certain to be produced by the red cells normally present. That sera so produced possessed very definite hemolytic and hemagglutinative properties capable of producing lesions (hemoglobinuria, thrombosis, liver necroses) which might erroneously be ascribed to the supposedly specific body was first suggested by Pearce[3] in a study of nephrotoxins and later[3] definitely demonstrated by a study of the action of sera prepared from the liver, kidney, pancreas, and adrenals completely freed from blood by prolonged washing through the blood vessels. Further, the study of sera so prepared and also of sera resulting from the injection of blood serum, bile, and urine, led to the conclusion that "the cells of various organs of the body have, while differing in morphology and function, certain receptor characteristics in common, and that one type of cell may therefore produce antibodies affecting several cells of differing morphology but with like receptor groups." Specificity in the morphological sense could not be demonstrated.

Other investigations with sera prepared from washed organs, especially those of Portis[4] (antithyroid serum) and Woltmann[5] also indicate the non-specificity of the cytotoxins.

Thus, while the study of the cytotoxins has aided and may still aid in the development of our knowledge of immunity and has incidentally offered several valuable methods of experimentally reproducing pathological conditions, it is evident that the sera produced by the injection of mixtures of organ cells have not a degree of specificity sufficient to warrant their further study in the hope of developing therapeutic methods.

Immunization to Nucleoproteids.

In order to prevent the adventitious formation of those bodies resulting from impure methods of immunization and also in the hope of obtaining greater specificity, a few investigators have utilized the proteid constituents of the cell.

Such attempts to produce antisera for somatic cells are limited, so far as we are aware, to those made by Marrassini,[6] Bierry[7] and his associates, and by Beebe. Of these studies the most comprehensive and most recent is that of Beebe.

Marrassini, working with the rabbit and guinea-pig, studied the effect of serum prepared by injecting rabbit's liver nucleoproteid. The changes resulting were, in general, degenerative in nature and similar to those caused by direct injection of the nucleoproteid itself, but usually more severe. The serum affected not only the organ for which it would be assumed it had an affinity, but also, to a greater extent, the kidney. Marrassini concludes that the action of a cytotoxin is of the same nature as that of other poisons of general action, such as potassium chromate, vinylamin, and pyrogallic acid, which are predisposed to affect more especially the excretory organs.

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The experiments of Bierry and his associates are few in number and reported but meagerly. In the first communication Bierry describes the action of a serum prepared by injecting rabbits with the nucleoproteids of the dog's kidney. The injection of 20 to 24 c.c. of the serum into the peritoneal cavity of a dog weighing 12 to 15 kilos caused, after three or four days, an albuminuria which reached its maximum on the 10th to the 15th day. The number of experiments is not stated, but mention is made of one dog in which an albuminuria persisted for one and a half months.

Later in association with Pettit, Bierry made a comparison between the action of liver and kidney nucleoproteid sera. Each was found to cause albuminuria and degenerative changes in both liver and kidney, but the kidney serum produced a more severe albuminuria and more marked histological changes in the kidney than did the liver serum. The lesions of the kidney are described as interstitial hemorrhage, congestion of the glomeruli, and granular degeneration of the cells of the tubules with granular tube casts; and those of the liver as congestion and granular and vacuolar degeneration. The authors concluded that the action of such sera is more energetic upon the organ from which the nucleoproteid is derived, but that there is also a definite action on other organs.

In the third investigation Bierry, assisted by Mayer, made a special study of the urine of dogs receiving a liver nucleoproteid serum. They found biliary pigments, lactic acid, and homogentisic acid and demonstrated that, in some instances, the urine had a marked reducing power not due to the presence of dextrose. By various experiments they were able to produce a condition which they considered analogous to alimentary glycosuria and due to the changes produced in the liver by the serum. The histological changes in the liver were those of granular degeneration and fatty transformation. The kidney and pancreas were normal. Albuminuria occurred in two animals, but was slight and transitory. These results appear to contradict those given by Bierry and Pettit in the earlier communication.

Beebe prepared a serum by injecting thymus nucleohiston of the calf which gave precipitin tests for both nucleohiston and nucleoproteid of the thymus. The more important sera were those prepared by treating rabbits with the nucleoproteids of the liver, kidney, and pancreas of the dog. These all gave definite precipitin tests with their respective nucleoproteids and caused agglutination of cell mixtures, but had no lytic action upon the same. They were all markedly hemolytic and hemagglutinative *in vitro* in dilution up to one to five, but did not cause hemoglobinuria when injected into animals.

In testing their cytotoxic action *in vivo* intraperitoneal injections of 2 c.c. per kilo of body weight were usually employed. The kidney serum caused albuminuria and acute degeneration of the kidney without changes in other organs. Albuminuria appeared generally on the fourth or fifth day, increased in amount rapidly and was accompanied by the excretion of abundant hyaline and granular casts.

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The liver serum caused granular and fatty changes and focal necroses of the liver with no changes in other organs or in the urine.

The urine of animals receiving pancreas serum caused what Beebe considers a partial reduction of Fehling's solution—"the formation of an abundant green precipitate, but not the typical red deposit of cuprous oxide." Albuminuria did not occur. Histological examination of the liver, kidney, and spleen revealed no changes; a study of the pancreas was impossible on account of imperfect fixation.

The results of these experiments (five with nephrotoxin, three with hepatotoxin and two with pancreas antiserum) provide, Beebe states, "strong indications that cytotoxic sera having a high degree of specificity can be prepared from the nucleoproteids of tissues," and that it is possible "to make a serum which will act primarily on one organ." Further comment on the work of Beebe will be made in the discussion of our own results.

METHODS.

As the amount of detail involved in work of this character is very great, it was considered advisable to limit our investigation to the study of two sera rather than to a superficial study of several. As physiological disturbances are the most satisfactory indications of the injurious action of a serum, antisera were prepared for the kidney and pancreas. The experience of practically all investigators that nephrotoxin is more nearly specific than other sera and the statements of Bierry and Mayer and that of Beebe concerning reducing substances in the urine also influenced this decision.

Rabbits, in groups of three, received in the peritoneal cavity five injections of the nucleoproteids of the dog's kidney and pancreas at intervals of five to seven days; after an interval of ten days the animals were bled. The serum thus produced was injected intravenously into dogs which had been under observation for considerable periods of time and the urine of which had been carefully examined daily.

As a control of the supposedly specific nucleoproteid sera, in order to determine if nucleoproteid serum may not have a general toxic action on animals other than that from which the nucleoproteid was prepared, rabbits were injected with the nucleoproteid* of the pancreas of the cow and the effect of this serum was tried on the dog.

As a further control, and in order to determine also whether or not antisera for nucleic acids could be obtained, rabbits were injected with the nucleic acids of the dog's pancreas and kidney.

The preparation of the nucleoproteids.—In the preparation of the nucleoproteids we have employed one of the methods recommended by Levene. This seemed particularly advantageous for two reasons. In the first place the heating of the glands to the boiling-point effectually eliminates all possibility of future autolysis, while on the other hand, the increased ease with which the solutions filter decreases the time of preparation. We are fully aware that the various nucleoproteids respond with different

* For this material we wish to thank Professor J. A. Mandel, of the University and Bellevue Hospital Medical School.

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degrees of ease to extraction, but the point we had in view was not to obtain the maximum yield of material, but to endeavor to produce in the shortest time the purest product possible.

Emphasis must be laid upon the fact that only blood-free organs were employed. In this direction extreme care was exercised since the exclusion of all proteids of blood origin must be of prime importance where specific gland products stand in question. By inserting a cannula into the aorta below the renal arteries and laying a ligature above the coeliac axis, an irrigation of $\frac{n}{7}$ NaCl solution was established by means of which the blood was thoroughly removed from the organs. The blood-free organs immediately removed from the animal and cut into fine pieces were pressed with a mortar and pestle through a fine-mesh sieve and the finely comminuted material mixed with from two to four times its weight of water. The gland in suspension was then brought to the boiling-point in an Erlenmeyer flask of appropriate size. After allowing the mixture to cool it was quickly filtered through a double-folded filter. The first few cubic centimeters of filtrate, invariably turbid, were thrown on the filter again until a clear fluid resulted. The product of from one to two hours' filtration might be said roughly to correspond to the amount employed in each preparation. To this was then added acetic acid until complete precipitation resulted, the amount necessary varying according to the kind of nucleoproteid. Under ordinary circumstances the nucleoproteid separated out as a fine white flocculent precipitate; only once did it become necessary to add alcohol to bring about the precipitation of this character. This precipitate was washed with distilled water by sedimentation until the washings did not respond to the biuret reaction. This procedure in the absence of a centrifuge such as that described by Beebe was accomplished in four to five hours. In order to hasten the process, siphonage of the supernatant fluid took place before complete sedimentation had been accomplished even at the risk of loss of material. The material was then suspended in water and put into solution with the smallest possible amount of sodium carbonate; the resultant solution when filtered gave a clear filtrate which was reprecipitated with acetic acid, washed several times by decantation, and dehydrated with alcohol and ether. The products were white powders. That derived from the pancreas contained 1.74 per cent P; from the kidney 2.10 per cent P.

Just previous to each injection the required amount of the powder was weighed out and dissolved in an appropriate amount of sterilized 0.5 per cent sodium carbonate into which solvent it passed readily.

It seemed to us distinctly disadvantageous that the substance should be kept in solution for any length of time even by employing cold or antiseptics as precautions against autolysis or bacterial action. That changes of a certain character do take place under such circumstances is evidenced by the fact that Beebe noticed that a fine deposit settled out in his solutions after some weeks. In only one instance in our investigation was the injection made later than a few hours after preparation of the solution. It would be hard to give absolute figures of the actual time consumed in the preparation of the various products. Excluding the

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period of cooling over night, when the gland stood in a condition free from the possibility of autolysis, the procedure occupied 15 hours, most of which time, however, the material was suspended in water. This period, especially in view of the fact of the initial stoppage of autolysis, would not allow sufficient time for change of the character so guarded against by Beebe. In our opinion this precaution is undoubtedly necessary, but not of the extreme importance assumed by him. The freedom of the products from blood or protoplasmic proteid impurities would seem to be the goal for which to aim.

If, with Kossel, we assume that the present nucleoproteids or nucleins are in part laboratory products not originally present in the cell but formed in the process of the separation, the proteid moiety of the compound must be derived from protoplasmic substance as distinct from the chromatin, but not necessarily different from the cell proteids (globulins or albumins). If such is the case the question as to the specificity of nucleoproteids as such must be ruled out and the proper direction to train investigation would be to attempt to prepare antibodies from various cell-proteids or nucleic acids prepared as pure as possible. The former point we still have in mind. As Beebe states, from the analysis of his preparations it is evident that the products employed by him are not true nucleoproteids but nucleins, and the molecule of the so-called protein nucleate possesses relatively less of the proteid and more of the nucleic acid radical. He also mentions that the color proteid reactions were given in only a feeble way. Certainly it would seem that the results obtained by the use of such products should be ascribed more probably to the nucleic acid than to the proteid radicals.

The products prepared by us contained less phosphorus than his, pointing to a higher proteid content, and gave characteristic results when tested with Millons, biuret, Adamkiewicz, and Molisch reactions. These reactions could not be ascribable to cell-globulins, which were removed in the process of preparation.

It seems rather dangerous to draw conclusions as to the intravenous clotting obtained when products prepared from organs containing blood are injected in the blood stream. The possibility is always at hand of the presence of fibrin ferment, thrombin, nucleohiston, or whatever may be the agent active in setting about the changes which result in the formation of fibrin in the blood. It is, we think, at present questionable whether it has yet been definitely shown that nucleoproteid, absolutely free from contamination of blood in the general sense, will cause intravenous clotting.

The preparation of the nucleic acids.—The method employed for the preparation of the nucleic acids from the pancreas and the kidney of the dog was essentially that of Levene. The finely comminuted gland was boiled for two hours in a 5 per cent solution of sodium chloride after which sodium acetate in the proportion of 7 per cent of the weight of the fresh glands was added and the mixture allowed to cool. Sodium hydroxide was next added in excess and the material allowed to stand over night. After the reduction of the greater part of the alkalinity with acetic acid the faintly alkaline mixture was precipitated with an excess

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of picric acid and acetic acid carefully added until a well-formed flocculent precipitate settled out. This filtered quickly. The amount of acetic acid necessary at this point varies according to the kind of nucleic acid. The proteid-free filtrate was next thrown in a large volume of 95 per cent alcohol, and allowed to stand until the nucleic acid settled out. The major part of the alcohol could be removed by siphonage and the precipitate collected on paper. The precipitate was again dissolved in alkali in the presence of sodium acetate and acidulated with acetic acid. A slight precipitate was filtered off. To the filtrate saturated with sodium chloride was added hydrochloric acid until the mixture reacted acid to congo red when an equal volume of alcohol was added. This precipitate showed itself to be biuret free and was dehydrated with alcohol and ether. The products contained from 8 to 9 per cent phosphorus. As was the case with the nucleoproteids, the necessary amount of the substance was dissolved in an appropriate amount of 0.5 per cent sodium carbonate and injected within a few hours after preparation.

Detail of Experiments and Results.

In all instances the dogs received in a small branch of the femoral vein a uniform dose of 2 c.c. of serum per kilo of body weight. The injections were made under light ether anesthesia and the experiment terminated by bleeding from the femoral artery under light chloroform anesthesia. In each group animals were killed at intervals of four, eight and ten days. Five animals received dog's kidney nucleoproteid serum;* five, dog's pancreas nucleoproteid serum; four, cow's pancreas nucleoproteid serum; three, dog's kidney nucleic acid serum; and three, dog's pancreas nucleic acid serum.

Histology.—In no instance did postmortem examination reveal definite macroscopic lesions. The histological study was limited to the kidney, pancreas, and liver. Tissues were fixed in formalin and in Zenker's fluid; the former were examined for fat by the frozen section and Scharlach R method, the latter were embedded in celloidin and stained by hematoxylin and eosin. Fatty changes were not constant, and, when present, of but slight degree. In the kidney nucleoproteid series, fatty changes were found in the kidney series once (10th day) and in no other organ. In the dog's pancreas nucleoproteid series very slight fatty changes were found in three—in one, in liver, kidney and pancreas; in one, in liver and kidney; in the third, in kidney only. The cow's pan-

* In preparing the various sera, the average amount of dog's kidney nucleoproteid to each injection was 0.11 gram; of the dog's pancreas nucleoproteid, 0.13 gram; of the cow's pancreas nucleoproteid, 0.15 gram; of the dog's kidney nucleic acid, 0.25 gram; and of the dog's pancreas nucleic acid, 0.11 gram.

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creas series gave negative results by this method. On the other hand, in the nucleic acid series fatty changes in the kidney were constant and well marked, affecting uniformly the loops of Henle. All the other organs were negative except for slight changes in the liver in one animal of the kidney nucleic acid series.

In the study of the Zenker hardened material, in no instance were changes in the pancreas found. The liver, although devoid of well-marked lesions, such as necrosis, almost constantly exhibited a peculiar change affecting all parts of the organ. This condition, which has been noted frequently by one of us as the result of the injection of various cytotoxins, and which unquestionably is that described by other investigators as a granular, vacuolar, or fatty degeneration is characterized by a swollen, pale, "washed-out" appearance of the liver cells with a few large, coarse granules and large irregular pale areas which stain but faintly or not at all. The latter areas are not of the character of fat vacuoles, but more irregular, vary considerably in size, and have no definite relation to the nucleus. The appearance is similar to that of liver cells containing glycogen, and as the same condition in marked degree was found in the adrenal, we are inclined to consider it as an abnormal accumulation of glycogen. Unfortunately this explanation did not occur to us until near the close of our experiments and proper routine tests were not made. Upon the basis of a single attempt to isolate the glycogen from the last dog of the kidney nucleic acid series, it can be stated, however, that a greatly increased amount of glycogen was present. This was determined by extracting the finely divided gland with hot water and filtering. The filtrate appeared milky white, gave the iodine reaction for the glycogen, which could be precipitated with alcohol at 65 per cent. No particular haste was employed in getting the organ into boiling water and the fact that the glycogen remained so long post-mortem points either to a large excess of the compound or perhaps to the absence or great diminution during life of the enzyme in the liver which transforms the glycogen.

The changes in the kidney were purely degenerative in character, of slight degree, and almost constantly present. The cells of the tubules, especially of the convoluted tubules, were swollen and very granular with more or less definite reticulum. As a rule the nucleus could be readily seen, but in the more marked conditions it stained poorly. Rarely the entire lining of a

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tubule could be seen separated from its basement membrane and lying free in the lumen as a poorly straining granular ring. In addition to these changes the tubules of the cortex, and less frequently, the straight tubules contained the finely granular reticulum so commonly associated with the milder disturbances of the kidney. In the straight tubules this material was often so compressed as to suggest finely granular casts, but definite casts were found but twice and only in the kidney nucleoproteid series. In the collecting tubules and especially in the loops of Henle, in some instances, a more or less marked vacuolization was present corresponding to the fatty change determined by the use of Scharlach R. In no kidney were glomerular changes found.

It is difficult to distinguish sharply between the types of kidney lesions caused by the different sera. In general the changes due to nucleoproteid sera were more severe and widespread than those due to the nucleic acid sera. The latter were characterized by a greater degree of fatty change and by a tendency to involve the loops of Henle rather than the convoluted tubules. If the presence of casts be taken as a criterion the lesions due to the dog's kidney nucleoproteid must be judged the most severe. It is a matter of considerable importance that the cow pancreas serum, in no sense specific, caused lesions in the kidney not to be distinguished from those due to other sera.

Examination of the urine.—The animals, fed on dog biscuit, were kept in cages suitable for the collection of their urine. This was examined daily for proteids and reducing carbohydrates. The clear filtrated urine was heated to boiling and the merest trace of acetic acid added. This indicated in a roughly quantitative way the amount of coagulable proteids (albumin and globulin) present. It is almost a constant occurrence to find traces of such appearing at variable and irregular times in dog's urine. By traces we mean that upon the addition of acetic acid a faint turbidity appears, which is in no sense a precipitate, but which in the course of 24 hours settles out at the bottom of the tube as a small light fluffy cloud. A second portion was tested with potassium ferrocyanide and acetic acid. The clear urine acidulated with the acid was treated with one drop of the dilute reagent. It was the unusual occurrence to find this test absolutely negative in the dogs under examination in this series of experiments and this result has been confirmed in the examination of many of the

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urines of other animals at different times. The urine of dogs, concentrated as it is in the passage of an excessively long system of tubules, carries down with it from the collecting tubules not inconsiderable quantities of proteids of the mucin and nucleo-albumin type, which show themselves by the latter test. At times the result of this reaction amounted to a definite flocculent precipitate. With the possible exception of the urines of two of our dogs injected with kidney nucleoproteid anti-serum we feel assured that at no time did our tests give evidence of an excretion of proteid which could in any sense quantitatively or qualitatively be ascribed to changes in the kidney.

In the case of Dog 14 injected on May 20 the urine collected on the 24th showed with heat and with potassium ferrocyanide a decided flocculent precipitate which would be called a positive reaction. The same is true for Dog 15 injected on the same day, the urine reacting positively to both tests on the 25th. Other than these, no results were obtained which would compare in any way to that described by Beebe, where 53 per cent of the urinary nitrogen appeared in the form of albumin. The quantity of proteid in the cases cited was so small that no attempt was made to determine whether it was an albumin or globulin. At no time were casts obtained in the urine, but upon histological examination of the kidney of Dog 15 as in one other dog (17) of this series, a few hyaline casts were seen in the tubules.

In a paper read this year before the American Medical Association by Robertson and Hacker, and based upon work done in this Laboratory, attention was called to the frequent appearance in human urines tested by Fehling test solutions, of a yellowish-green coloration which varies in intensity from the merest opalescence to a definite, finely divided precipitate which in the course of some hours settles out slowly to the bottom of the tube. It was then stated that this reaction is the result of the addition of too much urine in performing the test and must undoubtedly be ascribed to the presence in the urine at times of some weakly reducing compounds capable in large quantities of partially reducing copper solutions. This pseudo-reaction never occurs when there is employed a small amount of urine, sufficient, however, to show dextrose if present. In testing the urine of dogs these remarks are extremely to the point. When 10 or more drops of the filtered dog's urine were added to the two or three times diluted and boiling Fehling's solution and the mixture

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boiled a few seconds, it was not at all uncommon to notice in a few moments the appearance of a greenish-yellowish haze which gradually became more opalescent and opaque and which, in extreme cases, might resolve itself into a greenish or yellowish precipitate settling to the bottom of the tube, sometimes immediately, or, more frequently, if left standing, over night. This reduction is not due to dextrose; the urine showed no difference before or after fermentation, polariscopically; no osazone could be obtained, and Nylander's test resulted negatively. If on the other hand, only two or three drops of the urine were added to the diluted Fehling's solution in the ordinary way and not boiled after the addition of the urine the test remained negative. All of the urines tested for dextrose in the latter way, during the course of our experiments, showed absolutely negative results, while the pseudo-reaction was obtained more or less irregularly in 16 of the 20 dogs studied. In our opinion this pseudo-reaction has no direct bearing on the subject under discussion. In the case of one dog a continued pseudo-reaction was obtained which could be explained by the elimination of lactose following the removal of puppies during lactation. The negative results of Fehling's test with the urine of this animal indicated beautifully the fact contended for in the paper alluded to above, that Fehling's test performed as there advised can be employed without hesitation as a criterion for the presence of dextrose as against other reducing bodies. In none of the urines examined in these experiments was dextrose present in amounts which could be said to exceed the normal, granting that traces of reducing compounds, perhaps dextrose, do appear ordinarily.

While we cannot of course state positively, still it must be granted that it seems extremely likely that the reduction which Beebe describes as a "partial reduction of Fehling's solution" with "the formation of an abundant green precipitate" was nothing more or less than the pseudo-reduction which we have so frequently observed in the urines of normal dogs. As the manner in which his tests were performed or semi-quantitative details are not outlined, such explanations must be classed as only suggestive but not positive. It is our experience that the urines of the dogs injected with dog's pancreas nucleoproteid antiserum show no different character, as regards the content of reducing carbohydrates, than those treated with any of the other sera.

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Conclusions.

In so far as conclusions from so small a number of experiments are justifiable, our results do not support the theory that specific cytotoxic sera may be developed by the injection of nucleoproteids but indicate, rather, that such sera have certain mildly toxic properties acting in a general way and affecting especially the principal excretory organ, the kidney. In this regard we are in accord with Marrassini and in a general way with Bierry and his associates, but in direct conflict with Beebe's very definite statements.

It is clearly evident, however, that Beebe's claims for a specific pancreas serum based on the demonstration of reducing substances in the urine, especially in the absence of histological changes in the pancreas, is untenable in view of our experience with like reducing substances more or less constantly present in the urine of normal dogs.

We can make no definite statement concerning nucleoproteid hepatotoxic serum, as we did not prepare such, but it is difficult to explain the focal necrotic lesions of the liver, caused by Beebe's hepatotoxin, as a result of the action of a substance which should, presumably, affect the liver cells more diffusely. It may or may not be a matter of importance that his nucleoproteids were prepared from organs but roughly washed in running water and, therefore, especially as regards the liver, containing large amounts of blood. That a very toxic nucleoproteid may be obtained from red blood cells is well known and it is possible that, as a result, Beebe's serum may have contained hemolysin and agglutinin due to this substance, in addition to the supposed hepatotoxin, in sufficient amount to cause focal liver necroses through agglutinative thrombi, as has previously been described by one of us.[8]

Beebe states that all his sera "are markedly hemagglutinative and hemolytic *in vitro* in dilution up to one to five, but in dilution of one to twenty or above no difference is to be detected between the immune and the normal serum." The hemolytic and hemagglutinative powers of our nucleoproteid sera (the nucleic acid sera were not tested) were much weaker. Thus the dog's pancreas nucleoproteid serum, for example, had very slight power to hemolyze or agglutinate red cells. Two parts of the pure serum to one of dog's blood caused neither hemolysis

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nor agglutination, while 10 parts were required to cause but a faint hemolysis; with the same amount a very definite fine agglutination was evident only after five minutes. It would appear, therefore, by comparison, that the use of blood-free organs in the preparation of nucleoproteid sera lead to the production of a serum less hemotoxic than those developed by the use of unwashed organs. Under such circumstances, therefore, it is very important that future investigators of nucleoproteid sera work with blood-free tissues.

The changes in the kidney resulting from the administration of the kidney nucleoproteid serum, while very definite, cannot be considered as specific or even "special," for similar changes, often of the same grade, characterized the action of all other sera, even that prepared from cow's pancreas. These changes are, therefore, to be regarded as the effect of the excretion of toxic substances rather than as the manifestation of a selective action of the serum. It must be admitted, however, that it is difficult so to explain the severe albuminuria described by Beebe.

Finally, attention must once more be called to the importance, in all investigations of cytotoxic sera, of the use of blood-free organs, to the occasional occurrence of copper-reducing compounds in the urine of apparently normal dogs, to the not infrequent spontaneous nephritis in these animals, and to the possibility of albuminuria due to a catheter cystitis.

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THE CHEMISTRY OF ATHEROMA AND CALCIFICATION (AORTA).*

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This investigation owes its inception to an attempt to study by micro-chemical methods the sequence of the changes occurring in the experimental lesions produced in the rabbit's aorta by the administration of adrenalin. As however micro-chemical methods proved unsatisfactory and analytical methods impossible, on account of the small amount of substance in the rabbit's aorta, the work, as originally planned, was abandoned in favor of a study by analytical methods of the chemistry of the various stages of arteriosclerosis in the aorta of man. The studies of Klotz,[1] which appeared shortly after the beginning of the work, and those of Wells,[2] which were published previous to its conclusion, are so recent that they render a general survey of the literature of calcification unnecessary.

As this work has to do mainly with the relation of the fatty acids and lecithin[3] (phosphorus) to calcification, the results of Klotz and Wells have a very important relation and the views of these investigators may be briefly stated at this time. Klotz employing chiefly micro-chemical methods, believes he has demonstrated that the fatty acids play an important part in calcification. In a few qualitative examinations of calcified material he found what appeared to be calcium soaps. These observations he attempts to support by micro-chemical studies which, however, are not convincing. His demonstration of soaps depends on a peculiar staining with Sudan III, of calcium—principally upon a black discoloration with an aqueous solution of silver nitrate (Kossa's stain). The occurrence in close contact of granules staining by each of these methods is taken as evidence

* Conducted under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Med. Research*, 1906, xv.

[1] Klotz, O., Studies upon Calcareous Degeneration, I. The Process of Pathological Calcification, *Jour. Exper. Med.*, 1905, VII, 633.

[2] Wells, H. G., Pathological Calcification, *Jour. Med. Research*, 1906, xiv, 491.

[3] The term is meant to include all kinds of lecithins or lecithans.

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of the presence of calcium soaps and the conclusion is drawn that the formation of these soaps is the first step in the process of calcification. The inaccuracy of this method of investigation has been pointed out by Wells, who, using purely analytical methods, reaches a different conclusion. He finds there is no essential difference between the processes of normal ossification and pathological calcification. No evidence was obtained to indicate that calcium soaps form a constant and important stage in the process of calcification. That they may be present in small amounts is not denied. His experimental studies also speak strongly against phosphoric acid, arising from decomposed nucleoproteids, as an important binder of calcium.

Material.—The investigations here to be described deal with the study of nine aortas. Of these three were normal, two were aortas with extensive atheroma but no macroscopic evidence of calcification, and four showed various grades of calcification. One of these latter was the seat also of large "atheromatous ulcers." As several of the points studied have been covered by Wells' recent publication, these results will be stated but briefly.

Methods.—The preparation of the material was as follows: The entire aorta from heart to division of the iliacs was removed and the intima and media carefully separated from the adventitia in order to exclude all extraneous fat. The material was now cut into small pieces, dried in absolute alcohol over a water bath, ground to a powder, and then placed in a flask with reflex condenser and boiled with absolute alcohol for periods varying from twenty-two to fifty-four hours and afterwards extracted in the Soxhlet apparatus for from nine to thirty-one hours. To facilitate extraction, the material was reground every twelve to fifteen hours and fresh alcohol added. The powdered residue was now extracted in boiling chloroform from twenty-two to thirty-four hours and in the Soxhlet apparatus seven to fourteen hours. The use of ethyl ether, which was one of the solvents first employed had to be discontinued on account of the fact that numerous specimens reacted acid to phenolphthalein. Since this indicator served in the determination of the fatty acids, a neutral solvent became extremely essential. The extractive material taken up in absolute alcohol, boiling absolute alcohol and chloroform was in each case entirely soluble in these solvents. An analysis of the extract was then made for calcium soaps, fatty acids and

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lecithin as follows: To be absolutely certain of the solubility of calcium soaps, calcium stearate was prepared artificially. It was found to be sparingly soluble in cold absolute ethyl alcohol, considerably soluble in hot absolute ethyl alcohol, but insoluble in chloroform. According to Wells, "calcium oleate is less soluble in ether than in alcohol and the palmitate and stearate dissolve very little in ether, although considerably in ethyl alcohol; all dissolve much better in amyl alcohol, probably largely because of its high boiling point." According to the method of extraction, the calcium soaps should become soluble in the absolute alcohol and appear in the extractive material. The extracts were tested for Ca by fusing with sodium hydrate and potassium nitrate, precipitating with ammonium oxalate and weighing as CaO. The fatty acids were titrated in alcoholic solution with alcoholic $\frac{N}{10}$ NaOH using phenolphthalein as indicator.

Since the phosphorus contained in the alcohol-chloroform extracts was wholly organic in character, it could be considered that the P-content depended upon the presence of some form of lecithin.[1] The P_2O_5 content of the extracts was therefore determined by fusion, precipitation with molybdate solution, magnesium mixture and weighing as pyrophosphate and then calculated as distearyl lecithin. The remainder of the extractive material was estimated as neutral fats. The residue, remaining after extraction, was examined for Ca, Mg and P_2O_5 by the ordinary analytical methods. In making comparisons with other work, however, we must emphasize the fact that the residue of the entire aorta was used and not merely isolated calcified areas.

I wish here to express my indebtedness to Dr. Holmes C. Jackson, Director of the Laboratories of Physiological Chemistry and Experimental Physiology of the Albany Medical College, without whose instruction and supervision this investigation would have been impossible.

Results—I. Calcium soaps. As far as we were able to determine, no calcium soaps, or only mere traces, were to be found in normal or pathological aortas. This was definitely shown in the following manner. Extracts of the aortas which were completely soluble in absolute alcohol gave no reaction for calcium. Extracts, with supposed calcium content, dissolved in chloroform without leaving a trace of residue. As mentioned before the soap, calcium stearate, is insoluble in chloroform.

[1] DUNHAM, E. K., *Proceedings of the Soc. for Exp. Biol. and Med.*, 1904, I, 30.

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II. Fatty acids and Lecithin. These will be considered together.

NORMAL AORTAS.

	DRIED SUBSTANCE—PER CENT.		FATTY EXTRACTIVE—PER CENT.		
	CaO.	Fatty Extractive.	Fatty Acid.	Lecithin.	Neutral Fat.
1.....	1.4	20.3	6.1	18.3	75.6
2.....	.3	11.9	5.73	16.3	77.97
3.....	.....	.....	6.18	15.9	77.92

The surprisingly large percentage of lecithin is directly in line with the results obtained by Dunham* in his study of the normal kidney. He found that twenty-seven to thirty-seven per cent of the fatty extract was present in the form of lecithin.

Considering now the degree of calcification in the diseased aorta (the difference in calcification can be determined definitely by difference in calcium content of the residue) a striking relationship of the fatty acids, and especially of lecithin, to the grade of calcification is noticed. This is shown in the following table in which the analyses are arranged according to the calcium content; the last two being those in which no calcification was evident macroscopically.

DISEASED AORTAS.

	DRIED SUBSTANCE—PER CENT.		FATTY EXTRACTIVE—PER CENT.		
	CaO.	Fatty Extractive.	Fatty Acid.	Lecithin.	Neutral Fat.
1.....	11.9	22.5	9.6	16.6	73.8
2.....	7.5	30.	13.9	19.06	67.04
3.....	7.2	22.4	19.9	24.2	56.7
4.....	3.8	28.3	21.9	20.9	57.2
5.....	1.7	8.1	20.2	37.9	41.9
6.....	1.4	9.4	25.1	52.2	22.7

It is seen that the fatty acids and lecithin are present in greatest amount in the atheromatous aortas without gross evidence of calcification and that as the calcium content increases they rapidly diminish in amount. The remarkable increase in the amount of lecithin and fatty acids which appears at the initial stage of calcification certainly lends evidence to the fact of a decided "fatty" transformation occurring at this time. The fatty acids and lecithins here may or may not have a common origin. The parallelism in their appearance points to the probability that they

* Loc. cit p. 40.

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do. The fact that lecithin and fatty acids may arise from a decomposition of substances of the "protagon" type which Dunham has shown to exist in surprisingly large amounts in the normal cell further substantiates this idea. The second stage in the fatty transformation consists in the disappearance of the lecithin and fatty acids coincident with the increasing calcium content of the tissue. The fatty acids probably react with the alkalies furnished by the blood and pass out of the cell as soluble compounds. The lecithin undergoes decomposition, liberating its phosphate radical which serves either in part or entirely as the conjugant of the calcium.

III—*Neutral Fats.* The remainder of the fatty extractive was calculated as neutral fats. The results are shown in the above table. This procedure is not absolutely correct, since necessarily numerous lipoids were present; for example, beautiful tests for cholesterin were obtained.

IV—*The Residue.* Unfortunately, it was impossible to examine only calcified areas for calcium, phosphates and magnesium and at the same time to use all the material for fat analysis. Instead, the residue of the entire aorta was used. The entire P_2O_5 estimated was considered as combining with MgO and CaO to form $Mg_3(PO_4)_2$ and $Ca_3(PO_4)_2$. The remaining CaO was estimated as $CaCO_3$. In the aortas of lower calcium content, there was relatively a small quantity of $Ca_3(PO_4)_2$ while as calcification proceeded, the proportion of calcium phosphate to carbonate increased. For instance, in an aorta with estimated 3.8 per cent Ca content, the relationship between the $Ca_3(PO_4)_2$ and $CaCO_3$, was as 69.5 to 25; that with 7.5 per cent Ca content as 74.7 to 24.8; and that with 11.9 per cent Ca content, as 79.9 to 19.9.

As the calcification proceeded, however, the magnesium content decreased, being present in the more calcified areas as 0.1 per cent and 0.32 per cent.

Comparisons. Comparing our results with those of Klotz and of Wells:

1. They differ from those of Klotz, in that by analytical methods we were unable to find the calcium soaps which he claims to have demonstrated by micro-chemical examination but are in accord with Wells' results in this regard.

2. The inorganic analysis of the residue differs, however, from that of Wells. Possibly this is due to the fact that the entire aorta was used. Such material necessarily included both calci-

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fied and normal areas, thus diminishing the absolute percentage of calcification. Again Wells examined a different kind of tissue (lymph node) and it is not impossible that the somewhat higher P_2O_5 content obtained by him is due to the presence of the phosphorus containing proteids or their decomposition products which are known to be present in such tissue in relatively large amounts. The $Ca_3(PO_4)_2$ percentage was lower and the percentage of $Mg_3(PO_4)_2$ much less. The figures do not show the very close relationship to normal ossification which is so evident in his results.

Conclusions.

1. The absence of calcium soaps in the extracts of all aortas examined leads us to the conclusion that in pathological calcification, of the aorta at least, the formation of calcium soap is not an intermediate process.

2. The analyses of the residues apparently point to the fact, insisted upon by Wells, that in pathological calcification, the inorganic salts are deposited in approximately the same proportion as in normal ossification. This does not necessarily signify, however, that the initial processes, from which pathological calcification and normal ossification result, are identical.

3. The remarkably high percentage of lecithin in the initial stage of calcification and the fact that with increasing calcium content there occurs a coincident diminution in the percentage of lecithin has led us to suspect that the phosphate radical may be supplied from a decomposition of lecithin.

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ACTION OF CERTAIN DRUGS ON THE ELIMINATION OF URIC ACID DURING A NITROGEN-FREE DIET.*

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The extreme divergence of opinion which exists, based chiefly on a contradiction of experimental results, in regard to the metabolic disturbances commonly associated with the deposition of urates in specific localities of the body has frequently been the stimulus for further work along lines tending to the possible elucidation of this problem. It seemed probable to us that a fruitful line of inquiry lay in the attempt to determine what changes would appear in the nitrogenous composition of the urine of persons nourished with nitrogen-free food during the period of administration of such drugs (colchicum, sodium salicylate) as are most valued in the general treatment of gout or more especially of its seizures.

The fact that alcohol in its various forms apparently is a factor in causing disturbances in the normal elimination of the nitrogenous constituents of the urine and its well-known relation to the appearance of gouty tendencies influenced us to re-examine its effects with the view of comparison and possible confirmation of the work already carried out in this direction. In regard to the literature which has developed on these subjects within the past ten years it may be stated that many, if not all, of the experiments conducted before the time of our knowledge concerning the importance of the distinction between "endogenous" and "exogenous" eliminations, involving, as this does, the important question of diet, must be ruled out as useless. Experimentation is constantly hemmed in by faulty or inexact methods. Unfortunately each advance in the direction toward accuracy

* Work conducted under a grant made to the Bender Laboratory by the Committee on Scientific Research of the American Medical Association. Published also in *Jour. Amer. Med. Assoc.*, 1906, xlvii.

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sets the seal of questionable usefulness on older pieces of experimentation.

In the discussion we will here confine ourselves to the possible explanations of the results which have been obtained by others and those which we reached as the effect of the giving of alcohol, colchicum and sodium salicylate at a time when the nitrogenous elimination was, so to speak, of almost maximum endogenous origin, i. e., during the period of non-nitrogen diet.[1]

Our experiments were carried out on the writers and Dr. J. F. Robinson, assistant in surgical pathology in the Bender Laboratory, who kindly volunteered to aid us and to whom we wish to express our grateful indebtedness.

Diets.

During the preliminary purin-free period, the diet consisted of eggs, milk, potatoes and bread, the quantities being only approximated in the case of the three subjects and during the three days of the period. The results, however, were sufficiently in accord to serve as a satisfactory control for the subsequent nitrogen-free period. When the question arises as to the character of a diet which shall be nitrogen-free, we are confronted by the well-nigh impossibility of obtaining one, which shall serve as a palatable and savory substitute for the ordinary mixed diet while containing sufficient calorific value. For many persons the occurrence of nausea under such a diet precludes the possibility of its employment by them. Whether or not this is a psychic phenomenon is still somewhat questionable. The two principal objects to be attained in any such diet are that it be palatable and that by its absence an appetite be aroused, for, in the light of recent work, we can not but appreciate the extreme importance which must be attached to the psychic factors of digestion. These conditions unfortunately are hard to obtain. The usual ingredients of this diet are some form of pure starch, pure saccharose or other sugar and fat in the form of butter or thick cream. This combination has been employed by many investigators and especially by Pfeil,[2] Landergren[3] and by Folin[4]. The latter, referring to ar-

[1] We are of course well aware that to prepare a diet containing absolutely no nitrogen is well-nigh impossible. The term is constantly employed, however, as significant of the relatively low nitrogen content of the constituents when compared to the ordinary or even the meat-free diet.

[2] *Ztschr. f. physiol. Chem.*, xl, p. 1.

[3] *Skand. Arch. f. Physiol.*, xiv, p. 112.

[4] *Am. Jour. Physiol.*, xiii. p. 66.

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rowroot starch, which is commonly employed, gives it as his opinion that it is free from nitrogen and more palatable than corn or potato starch. The former statement is not strictly true, since nitrogen in small amounts can be detected in most samples of this type of starch. Relative to the degree of palatability of the starches as prepared by semidigestion with diastase (Folin) it can only be stated that it is a choice between evils of somewhat equal intensity. In any case, flavoring of some kind must be added to render it savory, after which it makes little difference what kind of starch has been employed. Without further discussion as to the diet suffice to say that, after personal experience, we decided that for our taste the daily diet most adapted to prolonged general use was the following:

Grams.	Calorific value.
250 arrowroot	957.0
140 pure cane sugar	504.4
50 butter	450.0
100 fat in the form of 250 c.c. of 40 per cent. cream	900.0
Sodium chlorid to taste.	2811.4

The whole daily allotment was prepared at one time, but was eaten in approximately three equal parts at the three meal hours during the day. The preparation took place as follows: The arrowroot was thoroughly stirred into 400 c.c. water in which the cane sugar and salt (about 20 gm.) had been previously dissolved. This was poured into a boiling mixture of equal parts of the cream and water and the whole well beaten under constant boiling for 20 minutes. At this point the mixture assumed the character of a blanc mange. The pudding was then flavored with various kinds of extracts and fruits. The presence of small quantities of nitrogen in the berries and fruits thus employed may account for the slight variations in the amount of nitrogen eliminated from day to day; the fluctuations, however, are not sufficient to affect whatever changes may have been noted.

From the thermodynamic standpoint the diet was ample. This fact is particularly evidenced by the rapidity with which the nitrogen elimination diminished during the starch-cream diet. On two of the subjects on the third day, and in the third on the fourth day, there was less than 3 gm. of nitrogen excreted during the 24 hours. These figures approach those of Siven[1] and of Landergren.

[1] *Skand. Arch. f. Physiol.*, xi, p. 308.

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METHODS.

The total nitrogen was estimated by the Kieldahl-Gunning method. The urea was determined by the Mörner-Sjoquist method, with the exception that in the sodium salicylate experiment a total nitrogen determination was made on the ether-alcohol filtrate (after the removal of the ether and alcohol) and from this quantity was subtracted that determined for the ammonia by separate analysis. Ammonia was estimated by the Shaffer method; uric acid according to the Hopkins-Folin method; creatinin by Folin's adaptation of calorimetric readings to Weyl's test. The calorimeter employed was made to order for us by Mr. E. C. Fasoldt, expert mechanician of Albany, N. Y., after designs with modifications according to the sketch by Van Hoogenhuyze and Verploegh.[1] This instrument reads to 0.001 inch (0.0254 mm.). Duplicate readings could easily be made to within 0.126 mm., which corresponds to .015 G. creatinin, according to Folin's calculation, giving results easily within the limits of error.

The inorganic phosphorus pentoxid was determined by titration with uranium nitrate, using potassium ferrocyanid as indicator. The organic phosphorus pentoxid estimation took place as follows: 100 c.c. of urine was evaporated to dryness, fused with sodium hydrate and potassium nitrate and on the fused mass the phosphorus pentoxid determination was made by the ordinary gravimetric method. The difference between this and the inorganic phosphorus pentoxid determination gave the organic phosphorus pentoxid. Total acidity was estimated by titration with sodium hydroxid, employing phenolphthalein with potassium oxalate, as suggested by Folin. Tables 1, 2 and 3 give the figures obtained in the analysis of the purin-free and nitrogen-free periods.

Before we take up the discussion of the main problem it may not be out of place to emphasize some few points which are brought out by the results of the starch-cream diet and also by a comparison of the latter with the purin-free period. In general the figures for creatinin may be considered as confirmatory to a certain degree of Folin's contention that in meat-free diets the elimination of this substance is independent of the amount of nitrogen excreted. No great variations occur in our figures, but they do, however, plainly indicate that the character of the diet

[1] *Ztschr. f. physiol. Chemie*, xlvi, p. 419.

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TABLE 1.—H. C. J.

Date.	Volume in c.c.	Sp. gr. 1.0—	Total Nitrogen, gm.	Per cent of Total Nitrogen as Grams Nitrogen eliminated as: Urea.	Ammonia.	Uric Acid.	Creatinin.	Undetermined.	P_2O_5. Inorganic, gms.	Organic, gms.	$\frac{N}{10}$ Acidity in c.c. — Acid. Total.	Remarks.
9	950	28	8.7	87.3 7.61	4.5 .398	1.5 .130	5.4 .443	1.3 .12	1.80	.....	.....	Purin-free diet.
10	815	25	9.6	89.5 8.55	3.1 .297	1.4 .138	4.7 .460	1.3 .15	2.17	.....	.....	Purin-free diet.
11	805	26	10.0	89.9 8.99	3.9 .397	1.2 .118	4.6 .464	0.4 .04	2.14	.....	.....	Purin-free diet.
17	430	25	4.8	75.2 3.61	6.8 .328	2.8 .133	10.6 .514	4.6 .21	0.93	.077	379.5	Starch-cream diet.
18	810	15	3.7	70.0 2.58	10.3 .382	2.5 .092	12.5 .464	4.7 .18	0.90	.050	216.0	Starch-cream diet.
19	650	15	2.8	58.5 1.64	13.7 .383	2.0 .055	15.7 .449	10.1 .27	0.90	.020	189.0	Starch-cream diet.
20	860	15	2.6	60.3 1.60	11.6 .308	3.9 .102	16.9 .449	7.3 .19	0.87	.077	171.0	Starch-cream diet + alcohol.
21	1115	15	2.4	58.3 1.43	14.0 .343	3.0 .073	19.1 .468	5.6 .14	0.82	.099	145.5	Starch-cream diet + alcohol.

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TABLE 2.—K. D. B.

				86.6	5.3	1.8	5.48	0.9	1.84	.....	.....	Purin-free diet.
9	1215	26	9.63	8.34	.512	.175	.526	0.9				
				87.1	5.3	1.4	5.6	0.6	2.46	.....	.....	Purin-free diet.
10	1200	24	9.24	8.05	.486	.128	.522	.6				
				86.1	4.7	1.7	6.1	1.4	2.08	.....	.....	Purin-free diet.
11	1295	14	8.94	7.70	.417	.149	.551	.12				
				72.4	11.6	0.52	10.2	5.3	.84	.....	161.3	Starch-cream diet.
17	1785	12	4.43	3.21	.515	.023	.454	.23				
				69.1	12.0	0.35	14.5	4.0	1.00	.....	154.8	Starch-cream diet.
18	1710	12	3.42	2.36	.411	.012	.497	.14				
				61.2	15.7	0.39	14.0	8.7	1.10	.....	184.6	Starch-cream diet.
19	1700	12	3.28	2.01	.516	.013	.461	.28				
				62.9	12.9	0.54	16.6	7.0	1.11	.....	88.4	Starch-cream diet + alcohol.
20	2550	05	2.97	1.87	.383	.016	.494	.23				
				66.2	11.4	1.00	16.1	5.3	.73	.....	115.5	Starch-cream diet + alcohol.
21	2570	05	3.08	2.04	.351	.031	.497	.16				

TABLE 3.—J. F. R.

				86.2	4.6	1.7	5.1	2.3	1.83	.....	.....	Purin-free diet.
9	550	32	9.06	7.81	.420	.157	.463	.21				
				89.5	3.5	1.2	4.4	1.4	2.25	.....	.....	Purin-free diet.
10	790	28	11.14	9.98	.392	.139	.498	.13				
				88.8	3.6	1.8	4.8	1.0	2.76	.....	.....	Purin-free diet.
11	900	28	9.08	8.07	.330	.162	.436	.08				
				79.0	5.5	1.8	9.3	4.3	1.03	.....	423.0	Starch-cream diet.
17	400	28	6.16	4.87	.341	.114	.576	.26				
				70.9	8.1	2.3	11.2	7.5	1.09	.....	273.0	Starch-cream diet.
18	980	24	4.17	2.96	.338	.099	.469	.30				
				55.9	13.5	3.3	18.2	9.1	1.07	.098	240.0	Starch-cream diet.
19	850	13	2.72	1.52	.369	.090	.496	.26				
				55.9	12.9	5.0	19.5	6.7	.82	.410	216.0	Starch-cream diet + alcohol.
20	825	14	2.52	1.41	.327	.128	.491	.17				
				54.3	14.9	5.4	22.4	3.0	.83	.055	186.0	Starch-cream diet + alcohol.
21	720	15	2.21	1.20	.329	.120	.496	.08				

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does exert in some manner a distinct though variable influence on the quantity of creatinin eliminated; further variations in creatinin elimination were also noticed, but these will be discussed later. Averages for the purin-free diet periods in the case of each of the three persons (A, B and C) are: Creatinin, A, 1.23 gm.; B, 1.43 gm.; C, 1.25 gm.; for the starch cream periods, of which there are two each for A and C: A, 1.13 gm. and 1.28 gm.; B, 1.26 gm.; C, 1.38 gm. and 1.33 gm. Considered as a whole, these figures might be regarded as lying within the limits of error. When the results for the individual days are examined it will be seen that only in two instances do the values in one series come within the limits of its comparative series, thus indicating differences which lie outside of the factor of their variability. This condition would tend to throw doubt on the statement made by the same author that the elimination value is constant for each individual, but different for different persons. This we could not confirm. Undoubtedly the explanation for this does not lie primarily in the character of the diet, but in the general condition of the cells of the body (endogenous metabolism) influenced secondarily by the diet, but not dependent directly on its nitrogen. In this sense Folin's ideas perhaps would find confirmation.

The effect of the nitrogen-free diet with its high calorific value is admirably shown when we consider the elimination of urea and ammonia, both in absolute quantities and in their relation to the total nitrogen output. In the purin-free period the percentage of the total nitrogen eliminated as urea varied from 86.2 to 89.9 in the three persons; the ammonia, from 3.1 to 5.3, figures which may be considered to be well within normal limits. The average for the control nitrogen-free period does not indicate as accurate a picture of the change inaugurated by the diet as would an inspection of the individual figures. However, the urea-nitrogen percentage of the total diminished to 55.9 and 79.0 per cent (last day of periods 55.9, 61.2 per cent) and the ammonia increased to 5.5, 15.7 per cent (last day, 13.5, 15.7 per cent). These figures are in complete confirmation of Folin's[4] results. In fact, they apparently answer the question propounded by this author as to the possibility of still further reducing the percentage of urea-nitrogen below the level of 60 per cent found by him. A glance at the figures in the tables will suffice to enable one to answer this interrogation positively. The constancy of the ammonia elimina-

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tion both in the purin-free and nitrogen-free periods is worthy, perhaps, of some attention.[1] This fact would indicate that under normal conditions a portion of the ammonia output does not stand in any direct proportion to the excretion of urea (endogenous elimination). Superimposed on this constant amount is that eliminated as the result of secondary influences such as diminution in the urea-forming function or acidosis. The effect exerted on the uric acid by the change from purin-free to nitrogen-free diet is equally interesting. The experiments of Burian and Schur[2] and, independently, of Siven and of Pfeil would tend to indicate that the uric acid elimination is independent of the total nitrogen output in purin-free diets. Folin's results stand at variation with this statement, and this author enters into a well-directed discussion as to the probable cause of this discrepancy. He concludes that not all of the uric acid eliminated during the so-called purin-free diet can be considered endogenous. We feel that our results show ample substantiation for this contention. There is a distinct and marked diminution in the absolute quantity of uric acid output during the nitrogen-free diet as compared with the purin-free period. In fact, in two of the three individuals the decrease was out of all proportion to the decrease in the nitrogen elimination, and hence there resulted an actual percentage diminution. The third case reacted similarly to those of Folin, in which there resulted an absolute decrease, but an increase in proportion to total nitrogen. Extremely interesting in connection with a possible explanation of these differences is the fact brought out by Folin that in a one-day change of diet from arrowroot to potatoes the individuals excreted more uric acid than on previous or subsequent days. As Burian and Schur's purin-free diet included potatoes, he suggests that perhaps the so-called purin-free articles of diet are not such in the sense of not causing the formation of purins. An examination of Folin's figures, however, indicates that not only is the uric acid, but also the creatinin and urea increased, and, more important still, the absolute quantity of ammonia markedly diminished so that the percentage output assumes almost that of the normal. If the potato diet merely affected the uric acid and indirectly the total nitrogen output the above explanation might be correct. In the light of the increase in urea

[1] Schittenhelm, C. P., and Katsenstein: *Ztschr. f. exp. Path. u. Therap.*, ii, p. 542.
[2] *Arch. f. die Gesammte physiol.*, lxxxvii, p. 239.

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and creatinin[1] and decrease in ammonia observed, it would seem as if a more probable explanation would be that the nitrogen content of the potato had simply caused the metabolism to return to the level of a higher nitrogen elimination which is under these conditions always accompanied by lowered percentage ammonia excretion. The basic content of the potato could not suffice to cause this change in the ammonia elimination. We will have occasion to return to this point when the effect of the drugs on the elimination of ammonia and uric acid is discussed. The inorganic phosphates suffered a decrease, while the undetermined nitrogen both increased in absolute quantity and in per cent of total nitrogen.

We have entered into this somewhat prolonged discussion of our control results mainly that there might be presented clearly the differences which appeared between the purin-free and nitrogen-free diets, placing special emphasis on the uric acid elimination in order that a basis should be established on which changes due to the drugs must be reckoned. Incidentally there has entered the necessity of confirming Folin's results. These we feel have been amplified while the several points become more distinctly drawn by the increased calorific value of the diet.

Action of Drugs.

A nitrogen-free diet, during which the nitrogen metabolism may be said to be strictly endogenous in character and reduced to its lowest minimum, appeared to us to present the best possible condition for the study of changes induced by the administration of certain agents about the effects of which on the elimination there are differences of opinion. It was hoped to obtain under such circumstances data which might be of service in throwing some light on the factors directly or indirectly implicated in the deranged metabolism.

Alcohol.

In view of the etiologic relationship which is thought to exist between alcohol in its various forms and arthritis uratica, it was thought essential to study the effect exerted by this substance on the relationships of the nitrogenous constituents of the urine excreted during the time of a nitrogen-free diet. Within the limits of this paper we can not discuss even in a meager manner the

[1] In both of the cases indicated the creatinin elimination on the potato days reached the level of the milk-egg diet.

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mass of literature, discordant in greatest part, concerning the chemistry of perverted metabolism in gout. It must suffice to confine ourselves to the effect produced by alcohol primarily on uric acid and secondarily on urea, ammonia, creatinin, the inorganic phosphates and the organic phosphorus elimination in the hope of eliciting facts that may throw light on the changes which occur.

The results obtained by various investigators in this direction are somewhat discordant and incomplete. The earlier work of Herter and Smith must be disregarded on account of the lack of knowledge at that time of the importance of regulating the diet. Again, all experiments concerning uric acid formation which are carried out on dogs can serve merely as confirmatory evidence, since we are aware of the distinct difference in nuclein metabolism which exists between dogs and man.

Later, the first well-devised experiments were those of Rosemann on a young man unaccustomed to the use of alcohol. His results do not find easy explanation. Suffice to say that 0.78 gm. of uric acid was excreted *per diem* during the 10-day alcohol period, as against 0.82 gm. during the control period. The 1,500 c.c. of 5 per cent alcohol added to the diet evidently not only did not increase the uric acid elimination, but tended to diminish it.

Beebe's carefully conducted experiments next appeared. In most of his experiments the examination of the urine was made hourly; alcohol pure and in its various forms was ingested both with and without food. The diets were rigorously observed, some of them containing purins and some purin-free. His deductions, which have a direct bearing on our topic, are as follows: In one experiment when alcohol (250 c.c. of 20 per cent.) was taken at one dose without food the hourly excretion of uric acid showed no change. A close examination of his figures might justify other conclusions, however. During the course of the experiment the hourly quantity of uric acid diminished from 30 mg. to 20 mg. and for three hours after the ingestion of the alcohol the subject was in a state of narcosis. Although the first hour after alcohol showed a decided decrease (from 31 to 26 mg.) in uric acid excretion, the following three hours averaged more than this (28 mg.). In view of the fact that a decided diminution was taking place in the uric acid output during the day, these figures might well be taken to indicate at least a tem-

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porary stoppage of that decline if not a positive increase. This experiment is not convincing. At the same time it must be admitted that Eschenburg[1] came to similar results, although his experiments were not so carefully carried out. On the other hand, Beebe found that both with purin-containing food and with a purin-free diet alcohol increased the elimination of uric acid, but that the increase was the greatest the larger the purin content of the food. In this Eschenburg also agrees. The increase, examined hourly, reached its maximum from 4 to 5 hours after the meal. Since the maximum increase as the result of the ingestion of food also occurs at that time, Beebe considers that additional proof is supplied for his conclusion, from the above experiments, that the increased uric acid excretion after alcohol is due to a disturbed metabolism of the purin constituents of the food.

While we have no results which are exactly comparable to his, the fact that on a nitrogen-free diet there took place a decided increase in the elimination of uric acid during alcohol ingestion must throw some doubt on the theory which Beebe advanced. In the following experiments the diet remained unchanged, but on the first day 300 c.c. of 25 per cent alcohol was taken in 7 doses at two-hour intervals during the day. No effect was noticeable, except that when the administration occurred at the time when the stomach was empty the usual sensation of warmth was felt; on the second day 200 c.c. of cognac containing about 50 per cent alcohol was ingested in 8 aliquot parts at two-hour intervals. This was without narcotic effect of any kind, and the subjects kept about their usual work in the laboratory (Tables 1, 2 and 3). From the figures of the tables, the following effects of alcohol may be readily noticed. Their general discussion appears later. A distinct diuretic effect, most marked in subject B, less so with J, and not noticeable in subject R (unaccustomed to alcohol) occurs. No proteid sparing action can be observed. A definite rise in uric acid excretion takes place (25 to 50 per cent). The elimination of ammonia undergoes a decrease. The creatinin output stands unchanged. There is marked increase in the organic phosphorus.

In our experiments the increased uric acid elimination might either be due first to an increased oxidation of purins of endogenous origin or, second, to an increased formation (synthesis) of uric acid, or perhaps, third, to a diminished oxidation of the uric acid.

[1] *Münch. med. Wochschr.*, xlvii, p. 2263.

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According to the first supposition, the quantity of purin bases eliminated should undergo a diminution in the proportion as they suffered an increased oxidation to uric acid. Unfortunately our determinations of the purin bases during these experiments were not sufficiently satisfactory or complete to warrant their presentation at this time. It can only be stated that no diminution apparently occurred; but we expect to verify this in a later publication. Beebe found an increased output of purin bases coincident with the augmented excretion of uric acid.

In the second supposition, if an increased synthesis occurred, changes should also have taken place in the other nitrogenous constituents or their antecedents which furnished the nitrogen for the synthesis. This did actually appear in that the ammonia elimination both absolutely and in its percentage of the total nitrogen diminished. Here again, our results are in direct opposition to those of Beebe, in which there was a decided increase in the ammonia output. While our periods were not as prolonged as his, still our figures are less variable, and the decrease in the three cases is, respectively, 6, 12 and 29 per cent. To correlate this fact with the increase in uric acid is somewhat difficult; perhaps they represent two distinct processes in no relation to each other. It is well known that the ammonia elimination stands in close relationship to the formation of acids in the organism, its function in part being that of a neutralization agent. Based on this idea, the diminished ammonia elimination would point to a diminished formation of acids from decreased decomposition of proteid or fats in the organism. In this case the diminished ammonia output would stand in no direct relation to the augmented uric-acid output. One noticeable effect due to the alcohol is the undoubted increase in the organic phosphorus elimination which occurred not only with alcohol, but after other agents (colchicum and sodium salicylate), which also increase the uric-acid output. Various attempts have been made to show that increased uric acid or purin elimination was followed by an augmentation in the quantity of inorganic phosphates excreted. This having proven impossible, attention has been turned to the organic phosphorus of the urine.[1] It would seem most plausible that in the formation of purin bodies, especially uric acid, from the nucleoproteid of the cell the phosphoric acid of the nucleic acid component

[1]Oertel: *Ztschr. f. physiol. Chem.*, xxvi, p 123; also Mandel and Oertel: *N. Y. Univ. Bull. Med. Sci.*, i, p. 165; Symmers: *Jour. of Path. and Bac.*, x, p. 159.

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should be eliminated, if not as an inorganic phosphate, perhaps in "organic" form, i. e., as nucleotin phosphoric acid,[1] and not determinable by reaction with uranium nitrate. Our results apparently point to this latter type of production and excretion, and hence in its relation to uric-acid formation the increased elimination would indicate that the augmented uric-acid output was dependent on an increased decomposition of phosphorus containing nuclear material (nucleoproteid, nucleins or nucleic acids) of the cell. In the light of this increased elimination of organic phosphorus pentoxid, the decreased output of ammonia occurring at the same time might be explained, as hinted above, by a diminished formation of acid radicles, perhaps phosphorus pentoxid. The figures in the table do in fact indicate that an actual decrease in the output of phosphorus pentoxid, precipitable with uranium nitrate, did occur.

Thirdly, that the increased elimination of uric acid is attributable to a decreased oxidation of this compound in the liver as supposed by Beebe seems hardly probable. At any rate, the results adduced by this author do not seem sufficient to strengthen the supposition. With the exception of the figures presented by him, we know of nothing which would tend to substantiate the deductions. By this it is not intended to imply that the liver may not be one of the seats functionating in the decomposition of uric acid, although this also has not been decisively proven. But it must not be forgotten in this connection that alcohol[2] and other uric acid increasing agents (colchicum, sodium salicylates,[3] etc.) tend to increase the activity of the liver and also its blood supply as shown by their acting as cholagogues. This certainly would speak against the view of an impaired function of this organ.

The creatinin elimination remained unchanged during the alcohol period. This fact would afford evidence against the view that the purins and creatinin have a common origin.[4] Nor could any nitrogen sparing effect be noticed, such as shown by the tables of Beebe. That the nitrogen elimination during the alcohol periods is less than that during the control period, we can not deny, since it is so evident. But a consideration in detail of the individual days in the previous control period will plainly indi-

[1]Schmiedeberg: *Arch. f. exp. Path. p. Pharm.*, xliii, p. 57.
[2]Salant: Proc. *Soc. exp. Biol. and Med.*, vol. i, p. 43.
[3]Kionka: *Ztschr. exp. Path. u. Therap.*, ii, p. 9.
[4]Burian: *Zeitschr. f. Physiol. Chem.* xliii. p. 546.

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cate that the nitrogen output was steadily diminishing and, unfortunately, had not reached its lowest level when the administration of the alcohol began. Hence we are more inclined to attribute the decrease noted to a continuation of the fall inaugurated in the previous period than to any effect of the alcohol. Also one of the subjects (R.) was unaccustomed to alcohol, and in his case we should not have expected the appearance of a sparing effect; it is evident, however, that it was just in his case that the most evident decrease occurred. The explanation probably lies in the fact that with the high calorific value of the diet the small amount of energy supplied by the alcohol was insufficient to alter the nitrogen elimination in an amount greater than the daily variation. The decreasing values in the control period just alluded to are also evident in the uric-acid excretion. On this account the increase in uric acid observed is much more marked than the average figures actually show.

Colchicum and Sodium Salicylate.

As far as we are aware no experiments have been recorded on the effect produced by these drugs on the nitrogenous elimination during a nitrogen-free diet. Many experimenters have considered the action of colchicum on the elimination of uric acid, especially in pathologic conditions, but the diets have been such or the methods employed were of such doubtful accuracy as to render it useless to quote them. The consensus of opinion, as indicated by statements in Cushny's text-book on "Pharmacology," seems to be united, however, in considering that uric-acid elimination is not increased after its administration, and that its use is purely empirical.

Concerning salicylates, the same statements hold true in general, except that the weight of evidence lies emphatically on the side of an increased output of uric acid as the result of their ingestion. Recently, however, Morgenbesser[1] reported experiments conducted on a normal individual, which apparently indicated a difference in the action of these compounds, whether on normal or on pathologic metabolism of uric acid. In a three-day period, during which 30 gm. of sodium salicylate were ingested daily, he noticed an increase in the nitrogen elimination of from 9 to 16 per cent. This increase is made up almost entirely of urea. The uric acid and purin bases were diminished, however.

[1] *N. Y. Med. Jour.*, 1906, lxxxiii, p. 760.

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TABLE 4.—K. D. B.

Date.	Volume in c.c.	Sp. gr. 1.0—	Total Nitrogen, gm.	Per cent of Total Nitrogen as Grams Nitrogen eliminated as: Urea.	Ammonia.	Uric Acid.	Creatinin.	Undetermined.	P_2O_5. Inorganic, gms.	Organic, gms.	$\frac{N}{10}$ Acidity in c.c. Total.	Leucocytes.	Remarks.
22	1410	08	2.37	60.3 1.43	13.9 .331	0.68 .016	18.5 .440	6.4 .16	.67	.....	115.5	.....	Starch-cream diet following alcohol.
23	1725	08	3.03	66.3 2.01	11.0 .334	0.53 .016	14.6 .443	7.5 .23	.78	.....	109.8	.....	Starch-cream diet + colchicum.
24	1455	08	2.52	60.3 1.52	15.5 .392	2.30 .058	17.2 .435	5.0 .12	.93	.....	100.5	.....	Starch-cream diet + colchicum.
25	1275	10	7.69	80.7 5.21	6.7 .515	3.5 .274	6.8 .529	2.3 .16	1.42	.....	142.5	.....	Meat diet.

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TABLE 5.—H. C. J.

22	555	20	2.70	64.0 1.73	10.7 .288	1.2 .032	16.6 .448	7.5 .20	.79	.045	147.0	.....	Starch-cream diet follow. alcohol.
23	615	21	2.36	59.7 1.41	11.8 .280	1.9 .045	18.4 .436	8.2 .19	.73	.038	145.5	.....	Starch-cream diet + colchicum.
24	1005	11	2.39	62.3 1.49	12.0 .287	2.9 .070	16.9 .404	5.9 .14	.92	.099	163.0	.....	Starch-cream diet + colchicum.
25	535	23	5.86	78.7 4.61	8.9 .523	2.8 .162	7.8 .464	1.8 .10	.86	.....	154.5	.....	Meat diet.
31	385	25	4.38	79.5 3.48	5.6 .249	1.3 .059	9.6 .425	4.0 .17	1.03	.....	163.0	.....	Starch-cream diet.
1	520	22	3.69	72.7 2.68	9.1 .337	1.1 .039	11.3 .420	5.8 .21	.87	.....	150.0	5600	Starch-cream diet.
2	575	23	3.14	69.8 2.19	10.0 .313	0.7 .024	13.3 .418	6.2 .20	.74	.....	154.5	5340	Starch-cream diet.
3	1300	14	3.36	72.3 2.44	9.8 .331	2.2 .075	12.5 .422	2.3 .08	.80	.....	199.5	5560	Starch-cream diet + sodium salic.
4	2000	10	3.05	67.2 2.05	8.9 .272	5.5 .167	13.1 .400	5.3 .16	.73	.....	120.0	6730	Starch-cream diet + sodium salic.

TABLE 6.—J. F. R.

22	470	21	2.06	56.3 1.16	15.2 .314	3.2 .066	22.8 .471	2.5 .05	.80	.012	183.5	.....	Starch-cream diet following alcohol.
23	1080	18	2.94	65.6 1.93	10.9 .321	4.1 .120	16.7 .496	2.5 .07	1.04	.135	222.0	.....	Starch-cream diet + colchicum.
24	1195	09	2.43	57.5 1.40	14.5 .353	2.8 .069	20.2 .492	5.0 .12	1.02	.113	196.5	.....	Starch-cream diet + colchicum.
25	825	21	6.89	79.5 5.38	6.8 .475	4.0 .278	8.0 .552	2.7 .20	1.25	.....	249.0	.....	Meat diet.
31	525	22	5.39	80.0 4.31	6.4 .346	1.9 .103	9.3 .502	2.4 .13	1.16	.....	255.0	.....	Starch-cream diet.
1	550	23	4.77	77.7 3.71	7.1 .339	2.0 .099	10.3 .495	2.9 .13	.88	.058	258.0	6150	Starch-cream diet.
2	750	22	3.70	71.6 2.65	10.6 .395	1.9 .072	13.4 .495	2.5 .09	1.00	.063	205.5	5340	Starch-cream diet.
3	850	22	3.04	66.1 2.01	13.5 .413	1.4 .043	15.8 .482	3.2 .10	.89	.105	244.5	5560	Starch cream diet + sod. salic.
4	950	20	2.64	61.3 1.62	10.9 .288	4.2 .112	16.3 .431	7.3 .19	.97	.068	261.0	6930	Starch-cream diet + sod. salic.

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In our experiments the colchicum was administered in the form of the wine taken on the first day at two-hour intervals, seven doses of 30 m. each. As no typical symptoms occurred, the next day the dose was increased to 40 m. Four such doses were taken, beginning at 8:20 a. m., when at 2 p. m., diarrhea set in; this, however, was counteracted by bismuth subgallate, but later characteristic symptoms, nausea, headache, etc., appeared and the drug was discontinued.

The sodium salicylate was ingested at similar intervals in doses for the first day of 5 gr. dissolved in water; in all, 45 gr. during the day. On the second day 10 gr. and 30 gr. doses were administered, making altogether 110 gr. The ordinary effects of buzzing in the ears and heart-burn, etc., were experienced. Tables 4, 5 and 6 indicate the result obtained by us.

Concisely stated, the figures show that both colchicum and sodium salicylates inaugurated a distinct increase (both absolute and in percentage of total nitrogen) in the output of uric acid probably not accompanied by a diminished purin base excretion. In the case of the salicylate the increase amounted to about 250 per cent. A coincident decrease in the ammonia elimination did not occur in the case of colchicum, but was distinctly evident in both subjects the last day of the sodium salicylate administration. The creatinin elimination also decreased at the same time. The figures are not concordant with reference to the total nitrogen output. With colchicum, two of the three cases showed a rise in the nitrogen elimination, but in one of them the increase did not occur on the day when the output of uric acid was maximum. The salicylate showed less effect, there being but a slight augmentation of nitrogen excretion in one case, and this when the uric-acid elimination was not at its height. We are inclined to believe that these drugs do not effect the elimination of endogenous nitrogen, at any rate not to the extent mentioned in the text-books. That they may cause an impaired internal assimilation of exogenous nitrogen and hence increased elimination, can not be denied. The unknown state of our knowledge concerning the factors which cause the excretion of creatinin under a creatinin-free diet renders a discussion of the results which we obtained somewhat vague and theoretical. The decrease in ammonia nitrogen and creatinin nitrogen observed as the effect of salicylates seemed to be offset by the increase in uric acid nitrogen and undetermined nitrogen. Just in what manner this rearrangement

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is brought about or its metabolic significance can only be conjectured.

The inorganic phosphorus pentoxid elimination remained unchanged. The fragmentary figures which we present as to the organic phosphorus pentoxid indicate an increase in the elimination. As in our previous discussion of this point in its relation to the increased uric acid output, we feel that additional evidence is added to the view that the augmentation in output is caused by increased production from nuclear material of the cell.

The acidity showed no change; no leucocytosis made its appearance during the administration of salicylates. The foregoing results have been substantiated by similar experiments by Dr. A. T. Laird on patients suffering with gout.[1]

Conclusions.

1. The elimination of uric acid on a purin-free or nitrogen-free diet is not a constant value for the same individual.

2. There appears to be evidence that the elimination of creatinin may be altered by conditions other than that of the creatinin in the food.

3. Alcohol increases the output of uric acid during a nitrogen-free diet; there occurs a coincident diminution in the elimination of ammonia; the organic phosphorus pentoxid excretion is also increased.

4. Both colchicum and sodium salicylate increase the output of uric acid, along with which takes place an augmented excretion of organic phosphorus pentoxid.

5. These facts seem to indicate that the rise in the uric acid elimination is caused by an increased formation as a result of augmented decomposition of nuclein-containing compounds of the cell.

6. From this it seems reasonable to decide that any agent which tends to cause an increased production of uric acid in the organism and thereby to increase its amount in the blood, must be contraindicated in those conditions where there exists a tendency for a deposition of urates to occur (gout). Probably the temporary beneficial effects of salicylates and colchicum observed clinically are the results of some secondary action possessed by them. That no permanent benefit results must be due to the fact that they are contraindicated.

[1] Results to be published later by Dr. Laird.

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EXPERIMENTAL MYOCARDITIS; A STUDY OF THE HISTOLOGICAL CHANGES FOLLOWING INTRAVENOUS INJECTIONS OF ADRENALIN.*

By RICHARD M. PEARCE, M. D.

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PLATE I.

During a recent investigation[1] by Dr. Stanton and myself of the lesions occurring in the aorta of the rabbit as the result of repeated injections of adrenalin, the heart muscle, in the few instances in which it was examined, was seen not infrequently to be the seat of very definite degenerative lesions and occasionally also of proliferative changes. The association of such conditions with an experimental vascular lesion suggested the possibility of producing experimentally a chronic myocarditis analogous to that seen not infrequently in man in connection with grave arterial disease. As the material at hand was insufficient for a comprehensive study a second series of investigations was inaugurated. In these an attempt has been made to study the sequence of the changes and to determine to what extent they are due to the direct action of adrenalin and to what extent secondary to the arterial lesions. Few of the investigators who have produced vascular lesions with adrenalin have described the associated myocardial changes. Fischer[2] mentions the occurrence of necrotic and fibrous changes and, rarely, calcification. K. Ziegler,[3] in a series of eight animals, found changes very similar to those hereinafter detailed.

Methods.—These were practically the same as in the earlier experiments by Dr. Stanton and myself, except that the initial dose was placed at one-tenth cubic centimetre, and rapidly raised to five-tenths and occasionally higher. All injections were made into the ear vein, and usually on alternate days. As previous experiments had shown that ten to twelve injections of adrenalin were sufficient to produce well marked arterial lesions, the injections in this series with a few exceptions were thus limited and the animals were then allowed to remain without further treatment for periods varying from one to three weeks. Thus the

* This investigation was conducted under a grant from the Rockefeller Institute for Medical Research. Read before the Johns Hopkins Medical Society, December 18, 1905. Published in *Jour. Exper. Med.*, 1906, viii, 400.

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animals which survived the treatment represent an average injection period of twenty-four days, and a total elapse of from twenty-seven to forty-five days, a sufficient time, as indicated by the few preliminary observations, for the development of proliferative lesions in the myocardium. The animals dying during the course of the injections furnished sufficient material for the study of early degenerative changes.

The histological methods were limited to the use of Scharlach R for frozen sections, and of hæmatoxylin and eosin and Mallory's connective tissue stain for material hardened in Zenker's fluid and imbedded in paraffin.

Results.—Thirty-six rabbits were injected. These may be divided into two groups: the first group including fourteen animals which died during the period of injection, and the second group, twenty-two animals, which received from seven to fifteen injections and were killed at various intervals thereafter. The first group represents animals receiving from one to five injections, of which none died later than the tenth day. All animals dying in this stage succumb apparently to circulatory and respiratory disturbance and present at autopsy acute dilatation of the heart, œdema and congestion of the lungs, and occasionally hæmorrhages from the serous and mucous membranes or in the interior of organs. No macroscopic lesions of the aorta are demonstrable. When death follows the injection within a few minutes the cardial dilatation, especially after the fourth or fifth injection, is extreme. Under such circumstances the heart loses much of its conical shape; the apex is more or less rounded and the overdistended auricles project laterally and greatly broaden the base. The left ventricle is very anæmic, and its pale almost bloodless substance is in sharp contrast to the blue-black color of the thin walled auricles.

Degenerative Changes.—The heart muscle of two of three rabbits dying within a few minutes after a single injection shows a well marked œdema causing more or less separation of the muscle fibres: in the third animal the œdema is slight. In all three the muscle fibres show irregular swellings, and the striations are somewhat indistinct. In one, multiple fractures of more or less homogeneous fibres are frequently seen, but as these conditions could not be found in either of the other hearts, they were considered as probably artifacts.

But one animal died after two injections. This death occurred

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on the fourth day, thirty-six hours after the second injection. The œdema of the myocardium is so great as to cause wide separation of the muscle fibres in many areas. In some of these areas the fibres have lost their striations and are very granular. A few small areas of intense œdema take a diffuse blue stain similar to myxomatous tissue.

Three animals died after three injections. The notes on one of these follow:

RABBIT No. 25.—Male, weight 1670 grammes. The initial dose was one-tenth cubic centimetre of a one to one-thousand solution of adrenalin injected into the ear vein. On the following day the dose was raised to two-tenths and after an interval of two days it was repeated. The animal was found dead seventeen hours after the last injection. At autopsy œdema and congestion of the lungs and extreme dilatation of the heart are present. Histologically the heart reveals focal areas of most intense œdema. These occur not only in the wall of the ventricle but also in the papillary muscles. Crossing these areas are strands of connective tissue in the midst of which fragments of heart muscle may occasionally be seen. Some of these fragments stain well while others are merely shadows of fibres in the midst of the finely granular coagulated serum. Some have ragged irregular ends pointing definitely to displacement by fracture. Elsewhere the fibres are widely separated by a serous fluid, are very granular, have swollen nuclei, stain lightly with eosin, and have but indistinct striations. On cross section many of the fibres show a clear zone about the nucleus, evidently a perinuclear œdema. Occasionally, bundles of fibres appear as if torn across, the space between being filled with serum. The branching of the fibres is brought out well by the œdema. Swollen hyaline fibres are not infrequent. The large blood vessels are widely distended; the capillaries on the other hand are not prominent. No lesions are seen in the walls of the blood vessels.

In a second animal of this period which received three injections of one-tenth cubic centimetre the œdema was not so prominent, but on the other hand more extensive granular and hyaline degeneration of the fibres was present. After the fourth injection one animal died and after the fifth, six. These last represent the period of greatest mortality as well as the gravest degenerative lesions. All animals dying at this time showed extreme dilatation of the heart and histologically, in addition to the changes just described, a severe granular and hyaline transformation with more or less necrosis and disorganization. This condition is illustrated by the following protocol:

RABBIT No. 6.—Male, weight 1720 grammes. On September 26, 29, and 30 one-tenth cubic centimetre of adrenalin solution was injected into the ear vein; on October 2 and 3, two-tenths. The animal died during the

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night of October 3. Upon post-mortem examination the heart was found to be dilated, the left ventricle pale and bloodless, and the lungs œdematous; the other organs were normal. Sections from three levels of the heart show general œdema and extreme disintegration of the muscle fibres. On both cross and longitudinal section the latter are seen to be irregularly swollen, granular, without striation, and not infrequently hyaline. The nuclei are swollen and frequently surrounded by a zone of œdema. In many fibres with extensive vacuolization of the protoplasm the nucleus does not stain. About such fibres small accumulations of mononuclear leucocytes are occasionally present and in some instances foci of epithelioid cells. In areas of extreme degeneration the outlines of the muscle fibres on cross section are indistinct and the picture is that of a uniformly granular mass with regularly placed lightly staining chromatic rings. These various changes affect the papillary muscles also. No changes in the vessels of the heart are demonstrable. Histological examination of the aorta is negative.

In other animals of this period the degenerative changes in the heart were of the same general character though varying more or less in degree. In two, a slight diffuse growth of connective tissue between the muscle fibres occurred.

Attempts to demonstrate fat in frozen sections of formalin hardened material treated with Scharlach R and counterstained by hæmatoxylin were uniformly negative. This method, however, revealed, in a few hearts, isolated fibres or small groups of fibres taking a diffuse yellow stain. These were more or less hyaline, and without nuclei; they however occurred in close relation to other similar fibres which did not thus react. This reaction has not as far as I am aware been previously described and its significance is not apparent.

The lesions in these hearts are due, manifestly, either to the direct toxic action of adrenalin upon the heart-muscle or to mechanical disturbances of the circulation caused by the effect of adrenalin on the vascular mechanism. They cannot be secondary to alterations in the walls of the large vessels, for in this series none of the animals exhibited macroscopic lesions of the aorta and in but three were degenerative changes evident microscopically.

Proliferative Changes.—Of the twenty-two animals surviving seven to fifteen injections, all but three showed degenerative changes in the myocardium, though seldom of the severe grade observed in the above descriptions. In twelve, more or less definite new connective tissue formation was evident. This new tissue was present, in some hearts, as focal accumulations of fine

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connective tissue about individual hyaline or granular fibres or about small groups of such fibres. In others a diffuse arrangement of new tissue was demonstrable in considerable areas of the myocardium, and in two cases a very severe and diffuse fibrous myocarditis existed. The new tissue as a rule was most abundant about the blood vessels but had no relation to the sub-epicardial tissue or to the endocardium. It was very prominent in the papillary muscles. All parts of the ventricle suffered, though if any difference existed, the lesions were more severe at the apex. Focal accumulations of leucocytes were not prominent in the more chronic lesions, though occasionally present in the earlier conditions. When present these were usually of the lymphoid cell type. No suppuration or other evidence of infection was seen at any time; the lesion apparently was a pure connective tissue proliferation following degeneration of muscle fibres. The following protocol is that of the most advanced lesion observed:

RABBIT No. 22.—Male, weight 1685 grammes. During a period of eleven days seven injections of adrenalin varying in amount from one-tenth to eight-tenths cubic centimetre were given (total amount five and two-tenths cubic centimetres). The animal was killed by chloroform five days after the last injection.

Autopsy.—Weight 1650 grammes. A small amount of clear serous fluid is found in the peritoneal and pleural cavities. The heart is large and firm; the walls of the left ventricle are distinctly thickened; the auricles are dilated. The entire circumference of the aorta at its origin is the seat of closely massed, depressed, round or oval, calcified areas which form a complete ring about the vessel and extend irregularly into the sinuses of Valsalva and along the ascending portion of the aorta for a distance of one and two-tenths centimetres. The orifices of the coronary arteries, in the natural position of the aorta, are entirely obscured but by pressure on the heart substance their presence is indicated by the escape of minute points of blood. These lesions cause considerable deformity of the vessel. A few isolated plaques of similar appearance are scattered elsewhere in the aorta and a considerable number are grouped about the origin of the cœliac axis.

Histology.—Sections through the entire ventricle from base to apex show extreme degeneration of muscle fibres and a new formation of connective tissue diffusely arranged, for the most part, but with here and there focal areas in which the muscle fibres are entirely absent. The muscle fibres as a rule are swollen, vacuolated, and exceedingly granular, though some are atrophied. Fibres with irregular constriction and swelling and more or less hyaline transformation are not uncommon. The nuclei are distorted, stain poorly, and frequently are entirely absent. In some fibres the nucleus is contracted and surrounded by a clear zone; in other fibres the nucleus is greatly swollen. The connective tissue is

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Plate I.

To Illustrate Dr. Pearce's Article "Experimental Myocarditis."

Albany Medical Annals, January, 1907.

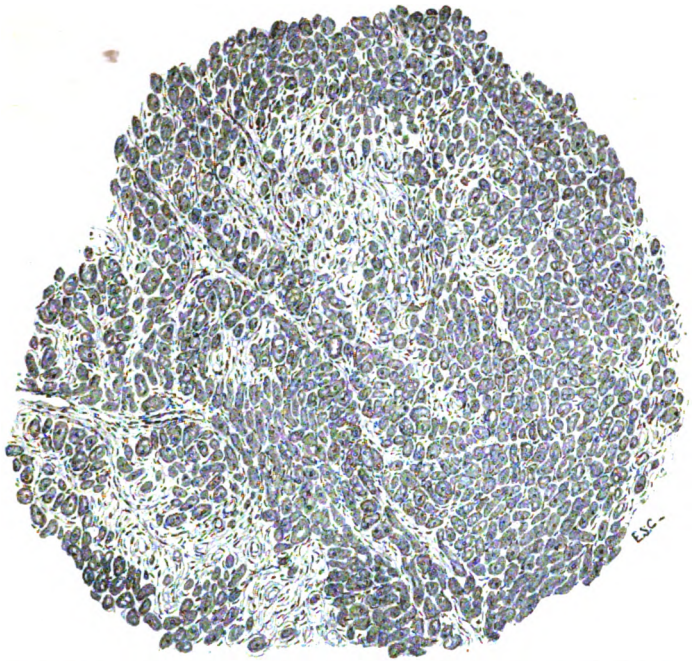

Fig. 1.—Fibrous myocarditis with more or less focal arrangement of the new tissue. Rabbit No. 22; see description in text.

Fig. 2.—Higher magnification of a different portion of the same section showing the character of the muscle degeneration and also a moderately diffuse increase of connective tissue.

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more abundant in the mid and inner portions of the ventricle and but slight beneath the pericardium and in the papillary muscles. The focal areas are more numerous at the apex of the ventricle and towards the endocardial surface. The connective tissue is very loose and œdematous. Between the elongated wavy vesicular nuclei is considerable intercellular substance practically free of lymphoid cells. While the arrangement of the new tissue is in general diffuse it is frequently more abundant about the blood vessels. In the focal areas the fibrillated character of the new tissue is very evident. The walls of the blood vessels show no change. Sections stained by Mallory's connective tissue method show everywhere between the muscle fibres a more or less well marked blue reticulum, while the focal areas take a deep stain relieved only by the deep red of fragments of hyaline fibres. The methods for demonstrating elastic tissue show a diffuse increase of fine elastic fibrils in the denser areas of connective tissue; they reveal no changes in the blood vessels.

Control Observations.—Although the literature treating of various experimental lesions of the myocardium of the rabbit contains no references to the occurrence of degenerative and proliferative changes in the hearts of apparently normal rabbits, it seemed advisable to determine definitely this point. As the sacrifice of a series of normal rabbits appeared undesirable the sections of heart muscle from a large number of animals injected with various organs and fluids of the dog during the past few years, in the course of several investigations of cytolysins, were utilized. A careful study of this material failed to reveal fibrous changes and showed few degenerative lesions. The latter were of slight degree and never of the type occurring after the administration of adrenalin.

Mode of Action of Adrenalin.—The association of a severe fibrous myocarditis with vascular lesions involving the orifices of the coronary arteries, as in the experiment given above in detail, suggests that the latter condition must have some causal relation to the myocardial changes. Indeed in the early part of the investigation it was thought that such a relation would eventually be demonstrated. Such, however, does not appear to be the case, for in one instance a myocarditis of equally severe type developed in the entire absence of lesions in the aorta. Moreover in six of the twelve animals exhibiting changes in the myocardium no lesions of the aorta were present, and in three of the remainder the lesions were but slight. The fibrous changes in the myocardium would appear therefore to be independent of the vascular lesions and not analogous to the myocarditis associated with arterial disease in man.

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Other possible explanations are based on a direct toxic action of adrenalin on the heart muscle, or an indirect action through the mechanical disturbances of the circulation which it causes. Although the physiological action of adrenalin on smooth muscle is well known we have no knowledge of its toxic action on the various types of muscle cells. Degenerative lesions in the parenchymatous cells and in muscle cells other than those of the heart and aorta are rarely seen, and it seems improbable that the toxic principle of adrenalin, if it exists, should be so selective as to affect only the muscle cells of the heart and the smooth muscle of the aorta and its larger branches. Indeed the limitation of degenerative lesions to the heart and larger blood vessels, and their practical absence in all other tissues, speak against any toxic action and point to an influence of a mechanical nature affecting these structures alone.

The action of adrenalin in constricting the arterioles with consequent increase in blood pressure is well known. This increase of blood pressure is alone not sufficient to explain the lesions, for if it were, we would expect the vascular changes due to adrenalin to be more general. But it is admissible to conceive of a temporary ischæmia of terminal vascular territories, due to the direct action of the drug upon the smooth muscle cells of the coronary arterioles, which lasts a sufficient length of time to cause some interference with the nutrition of the affected areas. From physiological experiments this period would appear to continue about ten to fifteen minutes. If to this we add the increased contractile effort of the heart necessary to overcome the greatly augmented intravascular tension, we have factors sufficient to explain the degenerative lesions of the early experiments. The heart muscle under conditions of poor nutrition is pushed to its extreme power and dilatation results with injury of single fibres or groups of fibres. This injury is due in part to nutritive and in part to mechanical disturbance. That the dilatation is extreme, that the muscle is anæmic, and that serious alterations of the fibres are associated with this condition after but a single injection of adrenalin has been repeatedly demonstrated during the course of this investigation.

Practically the same explanation was advanced by Dr. Stanton and myself to explain the necrosis in the lesions of the aorta due to adrenalin. K. Ziegler's explanation of the vascular lesions is also very similar. He points out that the inner and middle por-

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tions of the media of the aorta, the usual seat of necrosis, is the part of the vessel most scantily supplied by the vaso-vasorum and therefore most susceptible to necrosis at the time of vascular spasm and local anæmia.

Comparison with Other Experimental Lesions of the Myocardium.—The degenerative changes due to adrenalin do not conform in all respects to those caused by other agents used experimentally. The hyaline and granular changes in the muscle fibres, the alterations in striation, and the slight accumulations of lymphoid cells are similar to those found by various investigators (Comba,[4] Welch and Flexner,[5] and Mollard and Regaud[6]) who have studied the effect of diphtheria toxin on the heart muscle. On the other hand they differ in the absence of fatty changes, in the extreme œdema of the interstitial tissue, and in the disorganization of the fibres. In the same way also they differ from the lesions produced by Welch[7] in his experimental study of the effect of high temperature and from those produced by Ribbert[8] with staphylococcus pyogenes aureus, by Charrin[9] with bacillus pyocyaneus, by Tallquist[10] with streptococcus pyogenes, by Björksten[11] with various bacteria or their toxins, and by Flexner[12] with ricin and abrin.

With the exception of the slight focal increase of connective tissue described by Charrin, Comba, and Mollard and Regaud, as a rare result of repeated injections of bacterial toxins, the only form of fibrous myocarditis mentioned in the literature of experimental lesions of the heart is that following ligation of the coronary arteries. The histological changes following such ligation have been described by Kolster, Porter, and Baumgarten[13]. The last, in his very detailed description, states that by the fourteenth day the new connective tissue had largely replaced the widespread areas of anæmic necrosis. This is of interest in connection with the lesions above described, in that the most marked connective tissue proliferation occurred in a rabbit killed sixteen days after the first injection.

Relation to Lesions in Man.—No definite comparisons can be made. The animals with acute degeneration of the myocardium and extreme dilatation of the heart which die suddenly after the fourth or fifth injection represent a condition apparently similar to that occasionally seen in man, where unusual strain causes sudden death due to an acute dilatation of a heart previously injured by some toxic agent or disturbance of nutrition. The

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later fibrous lesions have no analogy to the commoner chronic forms of myocarditis in man associated with arteriosclerosis or following known toxic conditions. That some of the more unusual forms of fibrous myocarditis in man which are difficult of explanation may be due to circulatory disturbances of the same general nature as those caused by adrenalin injections in the rabbit cannot be denied. It is to these only that the results of this experimental investigation appear to have any relation.

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A NOTE ON THE PRODUCTION OF VASCULAR LESIONS IN THE RABBIT BY SINGLE INJECTIONS OF ADRENALIN.*

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The many publications which have followed Josué's demonstration of the power of adrenalin to produce degenerative changes in the rabbit's aorta have added much to our knowledge of the degenerative, infiltrative and repair processes which may occur in blood vessels, but unfortunately, from the point of view of comparative pathology, the value of this method of experimentation has been lessened by the failure to produce lesions entirely analogous to those of arteriosclerosis in man, the condition which it most closely resembles, and further by the absence of an adequate explanation of the manner in which adrenalin acts to produce such lesions.

This method, however, is so full of promise that it seemed advisable to continue the investigations[1] carried on in this laboratory, during the past two years, in the hope of producing, by varying the conditions of the experiment, lesions more closely resembling those of arteriosclerosis in man and at the same time to study by exact physiological methods the action of adrenalin. These studies are as yet incomplete and it is our intention in this communication to refer only to the lesions caused by single injections of adrenalin.

That repeated frequent injections of adrenalin are necessary to the production of experimental vascular lesions appears to be the opinion of all who have used it. Loeb and Githens[2] have stated that lapse of time is of more importance than frequency

*This work was conducted under a grant from the Rockefeller Institute for Medical Research. Published also in *Amer. Jour. of Med. Sciences.* 1906, cxxxii. 737.

[1] R. M. Pearce and E. McD. Stanton, "Experimental Arteriosclerosis," *Journal of Exper. Med.*, 1906, viii, 74; R. M. Pearce, "Experimental Myocarditis: A Study of the Histological Changes Following the Intravenous Injection of Adrenalin," Ibid. 1906, viii, 400.

[2] "The Effect of Experimental Conditions in the Vascular Lesions Produced by Adrenalin," *Amer. Jour. of the Med. Sci.*, 1905, cxxx, 658.

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of injections or size of dose, and although they alone appear to have noted this fact they did not materially limit the number of injections in their experiments.

Our attempt to produce lesions by single injections was mainly for the purpose of testing the theory offered by Pearce and Stanton and later supported by the former in his study of experimental myocarditis due to adrenalin. This was, briefly, that in both the aorta and the myocardium the primary condition is a localized anemia, due to the direct action of adrenalin on the arterioles of areas not readily supplied by collateral circulation. To this factor is added the influence of the strain thrown upon these poorly nourished parts during the height of the increase in blood pressure, an influence sufficient presumably to cause permanent injury. If lesions could be produced by single injections of adrenalin this theory would be strengthened and that of direct toxic action weakened.

As it had been previously shown that necrotic foci were present in the aortas of animals receiving four and five injections, three groups of animals were given respectively one, two and three intravenous injections of ½ to 1½ minims of a 1:1000 solution of adrenalin (Parke, Davis & Co.). Although lesions were produced in animals receiving two and three injections they became of little importance in view of the very positive results following single injections. Of ten animals in the latter series four died within a few minutes after injection; of the remaining six, one of which died at the end of seven days and five of which were killed after sixty-five to seventy days, all showed very definite vascular lesions. The protocols of these experiments may be briefly summarized as follows:

EXPERIMENT 13.—A full-grown rabbit received in the ear vein on December 9th, one half a minim of a 1:1000 solution of adrenalin. No ill effect was noticed after recovery from the initial disturbance. On December 16th, the animal was found dead. Postmortem examination revealed edema of the subcutaneous tissues, minute hemorrhages in the intestinal serosa and about 20 c.c. of slightly blood-tinged fluid, in the peritoneal cavity, but no increase of fluid in pericardial or pleural cavities. The heart was somewhat dilated and its muscle pale. Beneath the epicardium were numerous punctate hemorrhages. The aorta throughout the thoracic portions presented a peculiar wrinkled appearance without well-defined thickening or change in color. The other organs were not noteworthy.

Histological examination of the aorta at different levels revealed an extensive and diffuse degeneration of the media with more or less complete necrosis of the muscle cells and a straightening and fusion of the

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elastic fibres with a few angular bends. About two-thirds of the circumference of the vessel was involved and transversely the middle third of the media. In the heart muscle were focal areas of degeneration with slight increase of connective tissue and accumulation of lymphoid cells.

EXPERIMENT 17.—Rabbit weighing 1100 grams injected on January 4th with one half minim. Chloroformed March 14th; weight 1710 grams. Upon postmortem examination 75 c.c. of clear watery fluid were found in the peritoneal cavity. The aorta from its origin to celiac axis presented numerous irregular, calcified placques varying in size from 0.2 to 1.5 cm. in diameter. The other organs showed no changes. Upon histological examination the aortic lesions were those of degeneration and calcification.

EXPERIMENT 20.—Rabbit weighing 1920 grams injected on January 9th, with one minimum of adrenalin. Killed March 14th; weight 2120 grams. Postmortem examination revealed no lesions except in the aorta which from origin to bifuraction was dotted with oval and linear elevated areas of thickening and calcification. The areas were larger and more abundant in the ascending portion. Well-marked thickening was present about the orifices of the coronary arteries. Histological examination showed the usual picture of necrosis and calcification.

EXPERIMENT 21.—Rabbit weighing 2230 grams received on January 9th, one and one-half minims of adrenalin and was chloroformed on March 15th. At autopsy no changes were found except in the aorta which presented just above the celiac axis a single irregular area of a calcification 0.8 cm. in diameter. Upon histological examination very extensive repair was evident about the calcified area and especially in the subintimal tissues.

EXPERIMENT 22.—A rabbit weighing 1860 grams was injected on January 9th, with one and one-half minims of adrenalin. Chloroformed on March 15th; weight 1910 grams. In the aorta just above celiac axis are two calcified patches, the larger of which measures 0.5 cm. in diameter. The histological picture was that of calcification with no repair.

EXPERIMENT 23.—Rabbit, 1950 grams in weight, was injected January 9th. Killed March 14th; weight, 2700 grams. In the upper portion of abdominal aorta is one small wrinkled thickening 0.3 mm. in diameter which presents histologically, the picture of calcification.

These results, while they offer no explanation of the mode of action of adrenalin in producing vascular lesions, simplify the mode of investigation in that the problem is limited to the study of the effect of single injections, and comparisons may sharply be drawn between lesions so produced and similar lesions caused by prolonged administration of other substances, as nicotin, digalen and barium chloride.

It is evident, however, that in view of these results the theory of direct toxic action is hardly tenable, while that which recognizes a combination of vaso-vasorum disturbance, local anemia and vascular strain is greatly strengthened.

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A FURTHER STUDY OF THE EXPERIMENTAL PRODUCTION OF LIVER NECROSES BY THE INJECTION OF HEMAGGLUTINATIVE SERA.*

By RICHARD M. PEARCE, M. D.

(From the Bender Laboratory, Albany, N. Y.)

The observations herein detailed are supplemental to an earlier communication,[1] in which was described the power of the hemagglutinins contained in various cytolytic immune sera to form red blood corpuscle thrombi, and also the relation of the latter to necroses of the liver. In a later study[2] of the repair following lesions of the liver so produced, abundant confirmation of the earlier work was afforded. These observations, however, have not been generally accepted as conclusive. Though no other explanation of the necrosis has been offered, the masses of fused corpuscles in and about the necrotic tissue are still described by some investigators as artifacts, or as the consequence of post-mortem changes. It seems advisable, therefore, to present various control observations which offer very conclusive evidence in support of the views expressed in my first communication.

Without going into detail the lesions under consideration may be described as hyalin necroses, the position and extent of which vary according to the amount of serum[3] administered. Small doses cause focal lesions more or less isolated and irregularly distributed; large doses produce a diffuse necrosis which spares only the tissue about the larger portal spaces. The lesions are found only in the superficial portions of the liver, seldom in the deeper portions. In animals dying before the appearance of necrosis an intense congestion exists. Under such circumstances, the vessels are found upon microscopic examination to be distended by red blood corpuscles so closely massed as to present oftentimes a homogeneous appearance. The coalescence of red cells is very evident in the portal veins, while in the capillaries the occlusion leads to a distension so great that the columns of liver cells are more or less obscured. This congestion is less evident about the larger portal spaces. Endothelial cells, fibrin and bacteria do not enter into the formation of the thrombotic

*Conducted under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Med. Research*, 1906, xiv, 541.

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masses. An occasional leucocyte or endothelial cell may be seen, but as a rule these are absent.

Such observations have led me to conclude that the cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal vein by fused masses of red cells. To the effect of this obstruction, essentially a thrombosis, is added the pressure exerted by the perivascular edema and the over-filled bile capillaries. In parts of the liver midway between the larger portal spaces these factors are sufficient to overcome the pressure in the capillaries from the hepatic artery, and necrosis results; the cells in the neighborhood of the larger portal spaces, on the other hand, are preserved through a better blood supply, dependent, presumably, upon the greater arterial pressure in this region.

Although the rôle of the hemagglutinin in producing these necroses seems to me to be well established, it is necessary, as nearly all cytotoxic sera have manifold activities, to control by experiment other possibilities. Of these the most important are the action of the toxic products of hemolysis and the direct action upon the liver cells of some toxic substance in the injected serum.[4] This last seems improbable, as a recent study[5] of a number of cytotoxic sera, including hepatotoxin, has shown that the necroses do not result from somatogenic cytotoxins unless the serum has a high hemagglutinative power. Similarly sera of great hemolytic power do not cause necrosis unless the agglutinative power also is great. Moreover, it was shown that a serum of great agglutinative but no hemolytic power—that prepared by injecting bile—produces necroses as widespread and characteristic as those caused by sera of the highest hemolytic power. Nevertheless, as the sera which produce necrosis are, with the exception of bile serum, those which have great hemolytic activity, it seemed advisable to carry out various control experiments to determine whether or not this hemolysis had any share in the development of the necroses. It is to this phase of the subject that this communication is devoted.

Methods.—All attempts to remove from a serum its hemolytic activity, leaving only the agglutinative power, have been unsuccessful. The removal of this power by heating, so valuable in experiments in the test-tube, is not applicable to animal experiments, as the serum is activated by the complement of the injected animal. The action of chemicals and digestants affects

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the agglutinin as well as the hemolysin. The same is true of changes in serum due to lapse of time after withdrawal, and also of the serum of animals which are not bled for several months after the final injection. Even the positive results obtained by bile serum might be considered inconclusive owing to the possibility of a natural dissolution of the red cells after agglutination with the escape of toxic substances capable of causing necrosis. It became necessary, therefore, to determine what lesions might be produced in the liver by injecting the products of hemolysis and by producing experimental hemolysis by various substances having little or no agglutinative power. If such substances produced no necroses the theory of agglutinative thrombi would, in a negative way, be greatly strengthened.

Incidentally, numerous vital injections have been made to demonstrate that the masses of red cells do cause a complete obstruction of the vessels during life not only in areas of complete necrosis, but also at various periods preceding necrosis.

Experiments with the Products of Hemolysis.—I. To produce in the living animal a more or less continuous blood destruction, rabbits have been injected daily with normal dog's serum. Although this serum causes in the test-tube an agglutination of rabbit's red cells, this agglutination is very fine and disappears very rapidly as the result of the powerful hemolytic action which it possesses. Four rabbits were injected. Each received an initial dose of one cubic centimeter of serum in an ear vein, and the dose was gradually increased according to the condition of the animal. Two died on the twenty-first and twenty-second days respectively, the daily dose having reached ten cubic centimeters. The other two died on the thirty-sixth day, the dose having been suddenly increased from fifteen to twenty cubic centimeters. All showed the characteristic lesions of experimental anemia, *i. e.*, large swollen spleen, hyperplasia and edema of the lymph nodes, a diffuse dark red appearance of the bone-marrow, fatty changes in the liver, heart, and kidneys, petechial hemorrhages of the pericardium and lungs, edema of the lungs, and a hydremic state of the blood with lax clotting. The serum of one animal bled just before death was quite deeply colored by hemoglobin. In none of these animals could focal lesions of the liver be seen macroscopically. Histologically, all showed extreme granular and vacuolar degeneration, and one extreme fatty transformation. In none were areas of hyalin necrosis found.

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II. In a similar way dogs received intravenous and intraperitoneal injections of horse serum which, though powerfully hemolytic for dog's corpuscles, is but slightly hemagglutinative. Injections of this serum in doses varying from 1:800[6] to 1:280, and repeated every three to four days until four injections had been made, failed to produce focal lesions of the liver, although the presence of albumin in the urine and fatty changes in the kidney indicated the toxic action of the serum.

III. For the study of the effect of blood disintegration by a known chemical body toluylendiamin[7] was selected. This substance produces in the test-tube a slow hemolysis of the red cells, but no agglutination other than the mechanical massing of the cells after standing for several hours. Administered to the dog by the mouth it causes an exquisite experimental anemia accompanied by icterus. Six dogs received toluylendiamin with their food. Of these one was given a dose sufficient to cause death within twenty-four hours. The others were given small doses almost daily and sacrificed after one, three, five, six and eight weeks. The usual procedure was to begin with one-tenth of a gram and increase the dose very gradually to one-half a gram. When it was desired to terminate the experiment a fatal dose was given. Animals surviving a week or longer become emaciated and jaundiced, and albumin and bile appear in the urine. The blood[8] picture and the changes in the bone marrow, spleen and lymph nodes are those characteristic of experimental anemia.

The liver is of a greenish yellow color mottled with large, irregular yellowish or brownish areas. Its surface is smooth or finely granular, its substance firm and one section of a uniform greenish yellow color with smooth glistening appearance. In five of the animals of this group no trace of hyalin necroses similar to those caused by cytotoxic immune sera could be found upon either gross or microscopic examination. In the liver of the animal killed in the sixth week were found irregular focal areas of granular necrosis and extensive infiltration of leucocytes with the formation of a fibrin network. In these areas, which in no way resembled the necroses due to agglutinative thrombi, were masses of bacteria. They must therefore be considered as due to infection and not to the products of blood destruction. All the livers exhibited extreme granular and vacuolar degeneration amounting, practically, in some instances to necrosis of individual cells. The bile capillaries were greatly

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engorged with bile and could be followed easily both without and within the cells. No accumulated masses of red cells could be seen in the capillaries.

IV. Although the above experiments appeared to prove conclusively that the products of extensive hemolysis occurring in the living animal are not capable of causing necrosis in the liver, it seemed advisable to determine the effect of such products produced artificially. For this purpose eight dogs received injections of laked blood. The solution of hemoglobin was prepared from normal dog's blood by the addition of hemolytic immune sera. The first experiments were extremely unsatisfactory, for it was found that even after standing forty-eight hours the laked blood contained a sufficient excess of agglutinin to agglutinate red cells in the test-tube, and as it produced liver necrosis in injected animals it was impossible to draw any conclusions from such experiments. However, by centrifugalizing the fresh mixture of cells and serum after standing in ice for a half hour it was possible to remove in the supernatant fluid the excess of immune serum. Then, by diluting with salt solution and adding normal dog's serum to the residue, the hemolysin fixed to the agglutinated cells was able to complete the hemolysis at room temperature. The fluid thus procured was a rich solution of hemoglobin with little or no agglutinative power. The injection of this fluid, after standing one to four days, into the mesenteric veins in doses as high as sixty cubic centimeters (1:100), caused fatty changes in the kidney but no necrosis of the liver.

The Production of Necroses by the Injection of Agglutinated Masses of Red Cells.—In the earlier experiments on this subject several attempts were made to demonstrate the mechanical nature of the occlusion of the capillaries by injecting small amounts, five to ten cubic centimeters, of agglutinated corpuscles into the mesenteric veins. These experiments have been repeated with larger doses. Large amounts of blood agglutinated by an immune serum were allowed to stand in the cold for ten to fifteen minutes and then washed hastily by centrifugalizing in two changes of salt solution to remove the excess of serum. Fifty to eighty cubic centimeters of such a mixture have been injected directly into the mesenteric veins of dogs weighing five to seven kilos. In these animals hemoglobinuria occurs and necroses are found in the liver, but not comparable in number or extent to those produced by the serum itself. Those which do occur are,

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however, typical hyalin necroses. The occurrence of hemoglobinuria in these animals would at first glance appear to vitiate the experiment as it is possible to conceive of the necroses being due to the products of hemolysis and not to mechanical obstruction of the capillaries. Control experiments, however, demonstrated that the injection of the same amounts of normal defibrinated blood into the mesenteric veins causes hemoglobinuria of equal degree but no lesions in the liver. It therefore seems fairly conclusive that the necroses following the injection of clumped corpuscles are due to mechanical obstruction, and that in the production of these necroses the products of the associated hemolysis play no part.

Demonstration, by Vital Injections, of the Occclusion of the Liver Capillaries.—In order to demonstrate that the masses of fused red corpuscles do actually occlude the blood vessels, a series of nine animals, which had previously received hemagglutinative sera, have been injected with carmine during life. For this purpose an ammoniacal solution of carmine, prepared according to the formula of Chrzonszczewsky,[9] was prepared and injected as nearly as possible under natural conditions of pressure.

This preparation penetrates readily the capillary system of all organs and is of especial value in demonstrating occlusion of the capillaries of the liver. With animals under ether anesthesia, ten to twenty cubic centimeters of ammoniacal camine were injected into the hepatic artery, into the veins of the mesentery, and into the femoral vein at various periods after the injection of the agglutinative serum. For detailed study frozen sections of formalin-hardened material stained in hematoxylin have given the best results. In no instance have pigment granules been found in the vessels of the necrotic foci, though they are seen closely packed in the vessels about such areas. The lesions in all these animals were of the diffuse type and there was considerable evidence to indicate that not only the capillaries, but branches of the portal system of considerable size, were occluded. Similar injections made four hours after the introduction of the agglutinative serum penetrate the superficial portions of the liver to but a slight extent and very irregularly, whereas under normal circumstances such injection produces a diffuse impregnation. It seems conclusively proven, therefore, that the fused masses of corpuscles cause a mechanical obstruction to the circulation.

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No attempt has been made in connection with these injection experiments, mainly because the necrotic lesions were so diffuse, to determine the relation of the smaller focal lesions to the vascular systems of the lobule. Considerable evidence is at hand, however, to indicate that the immunity to necrosis of the tissue immediately about the larger portal spaces, a condition constantly seen in the diffuse lesions, is apparently due to the influence of arterial pressure. Opie[10] has recently shown by injection experiments that the greater pressure of the arterial blood supply in the periphery of the liver lobule is sufficient to keep this portion of the lobule practically free from injected particles of foreign material, thus explaining the relative infrequency of necrotic lesions in this area. It appears plausible that the same theory applied to the blood supply of the tissue about the portal spaces would explain the immunity of these areas to necrosis. All evidence indicates that the cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal veins by fused corpuscles. The mechanical pressure exerted by the perivascular edema and the distended bile capillaries probably aids the occurrence of necroses by neutralizing, in part at least, the pressure in the capillaries derived from smaller branches of the hepatic artery. The necrosis occurs uniformly in those portions of the liver in which no large vessels are present. In portions in which the latter are present, as the neighborhood of the portal spaces, the arterial pressure is sufficient to preserve the circulation in their immediate neighborhood, while the tissue at a distance is destroyed. Only thus is it possible to explain the normal tissue in the midst of large necrotic areas. The same difference in pressure may explain also the greater extent of the necrosis at the periphery of the liver.

Conclusion.—Whether or not red blood corpuscle thrombi may be concerned in the focal necrotic lesions of man, a question which has been discussed elsewhere,[11] it would appear to be definitely established that such thrombi do occur in the experimental lesions caused by sera possessing hemagglutinative power and that, aided perhaps by the associated perivascular edema and the engorgement of the bile capillaries, they produce necroses of the liver. That the capillaries of such areas are actually occluded by fused red cells is demonstrated by the experiments here described, as is also the inability of the products of hemolysis to produce such necroses.

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4. In this connection also must be considered the question of autolysis. It is possible that through either some substance in the injected serum, or some substance formed in other organs as the result of altered metabolism, the synthetic functions of the liver cells are destroyed, but not the autolytic ferments, and that, through the activity of the latter, destruction of the cells occur. The resemblance of the lesions to those of acute yellow atrophy and allied conditions in man is very suggestive. Chemical studies based on this supposition are now under way.

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REGENERATIVE CHANGES IN THE LIVER:

A STUDY OF EXPERIMENTAL LESIONS IN THE DOG.*

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PLATE II.

Elsewhere[1] I have described a form of experimental cirrhosis which in its nature is essentially a repair of extensive but more or less irregularly arranged necroses produced by the action of hemagglutinative sera. To this account the present communication is more or less supplemental in that it deals with some of the more important of the finer details of the regenerative

*Conducted under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Med. Research*, 1906, xv, 99.

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process, which, for the sake of brevity, were merely outlined in the earlier communication.

The reparative process to be described is of peculiar interest in that it follows definite necrotic lesions produced by an agent reaching the liver through the circulation and not those caused by direct mechanical injury. For this reason, and also because of the resemblance of the early necrotic lesions to acute yellow atrophy and of the later reparative process to cirrhosis, a comparison with the regenerative processes in the liver of man is possible.

Our knowledge of the regenerative changes in the liver is based mainly on the studies of the repair following mechanical injuries and that occurring in acute yellow atrophy and, to a lesser extent, in cirrhosis of the liver. The principal experimental studies[2] since the introduction of aseptic methods and the development of our knowledge of indirect cell division are those of Podwyssozki,[3] Ponfick,[4] and v. Meister.[5] A comprehensive review of the reparative process in acute yellow atrophy may be obtained from the writings of Meder,[6] Marchand,[7] Stroebe,[8] Barbacci,[9] and MacCallum,[10] while the regenerative changes in cirrhosis, first emphasized by Kretz,[11] have since been studied by MacCallum[12] and Kelly.[13]

Podwyssozki, who has made the most comprehensive study of the repair of wounds of the liver produced in various ways, concludes that small losses of substance are repaired, without the formation of fibrous tissue, by proliferation of the liver cells and the cells of the small bile ducts. In more serious injuries in addition to such proliferation a more or less abundant formation of connective tissue occurs. In his studies he used the rat, cat, rabbit and guinea-pig. The formation of new liver cells by mitosis begins after twenty to forty-eight hours and mitotic figures are very abundant by the fourth to the seventh day. Mitoses are also seen in endothelial and connective tissue cells and in Kupffer's cells. The newly formed liver cells are usually large and pale and of round or oval shape. The bile ducts, especially the interlobular, proliferate freely and from them new liver cells may develop directly or they may form large, irregular sprouts in which multinucleated masses of cells appear and from which new liver cells separate. Podwyssozki emphasizes the similarity of the repair of liver cells in pathological conditions to their embryonic development.

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Ponfick's experiments, which were repeated by v. Meister, demonstrate that after extirpation of large portions, three-quarters to four-fifths, of the liver of the rabbit a hyperplasia of the remaining substance causes a restoration of the liver to its original size. This proliferation, which is characterized by the formation of lobules of unusual size, is a condition analogous apparently to the vicarious hypertrophy of paired or multiple organs and is due almost entirely to a regeneration of liver cells. Mitoses were first observed after forty-five to seventy-two hours and soon became very abundant. Large, pale, finely-granular cells, often with two nuclei, were very numerous and apparently represent newly formed cells. In the bile ducts and blood vessels also was seen evidence of proliferation, though mitotic figures could not be readily demonstrated.

The so-called adenomatous nodules ("multiple knotige hyperplasie") described by many investigators, and studied especially by Marchand and Barbacci in connection with acute yellow atrophy and cirrhosis, may be considered as the result of a hyperplasia comparable to that produced experimentally by Ponfick and v. Meister. A similar hypertrophy of massive character has been observed by Ponfick[14] in association with echinococcus cyst.

Practically all who have studied the repair process in acute yellow atrophy are in accord concerning regeneration by mitosis of surviving liver cells, but some difference of opinion exists in regard to the solid and tubular cell-strands usually described as newly-formed or pseudo bile ducts. All recent investigators have abandoned the idea that these structures are atrophied rows of liver cells and consider them as sprouts from the small interlobular bile ducts growing into the necrotic lobule. By a gradual transformation of the cells of such sprouts true functioning liver cells are formed. Marchand, however, states that similar structures may also be formed by the proliferation and fusion of the true liver cells in small islands of liver substance which have escaped the general destruction. This latter view Stroebe considers unproven and MacCallum in the one case which he studied was not able to demonstrate this form of proliferation.

The recent studies of regenerative changes in cirrhosis of the liver were undoubtedly suggested by Kretz's statement that this disease is the result of successive processes of repair following repeated focal degenerations of the parenchyma. These studies treat of changes in the size, shape and internal arrangement of

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the lobule, of its altered blood supply, and of the origin and appearance of the newly-formed cells. In general, the proliferation is similar to that in acute yellow atophy, but, owing to the chronicity of the lesion as seen at autopsy, mitotic figures are rarely found in the parenchymatous cells. The new formation of such cells, however, is indicated by the occurrence among cells of the usual appearance of large, clear, round, plump cells with two or more nuclei and devoid of fat and pigment. What has been said of the newly-formed bile ducts in acute yellow atrophy holds for the similar structures found in cirrhosis.

The present study is based on material from the livers of sixteen dogs representing periods varying from thirty-eight hours to thirty-six days after the injection of the serum. As the larger portion of the animals died during the first week, it is possible to present an accurate account of the sequence of reparative changes to the end of the seventh day. The late changes are also well represented by those animals which survived the acute disturbance. The middle period, however, is not well represented.

The degree of repair has been found to vary considerably at any given period. This is particularly true of the group of five animals representing the period of forty-eight to sixty hours. This difference appears to be dependent in part upon the extent of necrosis and in part upon the general condition and age of the animal. It has been observed, not infrequently, in animals not included in this series that when extensive necrosis of the liver was associated with severe general disturbances, indicated by marked hemoglobinuria and exhaustion, no repair was evident even in those animals surviving to the end of the second day. These various influences have been emphasized by Podwyssozki, who found that mitoses are most abundant when the conditions of nutrition are best. Thus he found mitosis to be delayed in starved animals, after considerable loss of blood and in old animals. In the latter they may fail to appear, as may they also in the neighborhood of suppuration. They are very seldom seen at the margin of areas of complete necrosis.

The primary necrotic lesion may be described as follows: After twenty-four to forty-eight hours the liver presents a uniformly mottled appearance; fine, irregular, yellowish brown or grayish yellow, non-elevated areas being sharply separated from deeply congested or occasionally even hemorrhagic areas. On

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section the brownish portions have a distinct hyaline appearance. The superficial portions of the liver are uniformly more extensively involved than are the deeper portions, though in some of the small lobes the necrosis may be quite general. Histologically, the necrosis, which is hyaline in character, may involve all portions of the liver tissue except circular areas of varying size in the immediate neighborhood of the larger portal spaces.

In the necrotic areas the destruction, as far as the hepatic cells are concerned, is uniform and complete; the cells of the capillaries may, however, persist. A narrow ring of liver cells with vacuolated protoplasm and pyknotic nuclei separates, as a rule, the necrotic from the normal tissue. Leucocytic infiltration may or may not be present. The capillaries of the necrotic tissue are widely dilated and tightly packed with swollen and distorted red blood corpuscles which may occur in masses or may retain distinct outlines. In the congested portal veins, on the other hand, the fusion is quite constant, the plugs for the greater part having a distinctly hyaline appearance. The perivascular spaces of the capillaries are distended with serum, and the bile passages of all sizes are, as a rule, dilated and engorged with bile.

The earliest evidence of repair, as indicated by karyokinesis of parenchymatous cells, is seen in the liver of an animal which died exactly thirty-eight hours after injection. The necrosis in this instance is very diffuse and accompanied by slight leucocytic infiltration. The destruction of liver as well as endothelial cells in the affected areas is complete. Between the completely necrotic cells and the normal cells is seen a rim of cells two or three deep in which the cell structure is more or less preserved; in these the nuclei are visible but the cell protoplasm is very granular and contains many vacuoles. It is noteworthy that mitoses are not found in such cells but only in the well preserved cells beyond (see Fig. 1). They are very few in number and are found only after prolonged search. This agrees with Podwyssozki's observation that mitoses occur only in perfect cells at a distance from the necrosis. There is some evidence, however, as will be shown later, that the nuclei of apparently degenerated cells, at the edge of the necrosis, may divide by direct division to form multinucleated protoplasmic masses. There is no evidence at this period of proliferation of the endothelial or connective tissue cells or of the cells of the bile ducts.

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The period from forty-eight to sixty hours is represented by material from five animals. In these the repair is of the same general character but differs somewhat in degree. Aside from the mitoses of liver cells, which are more abundant, the most striking change is the proliferation of the cells of the supporting framework. The necrotic foci are, on all sides, separated more or less from the normal liver cells by a zone of closely massed newly-formed endothelial cells (see Fig. 2). Proliferation of the same cells occurs in the persisting capillary framework in the midst of the necrosis. The nuclei of these cells, although distinctly vesicular in character, are rich in chromatin and stain deeply. The protoplasm as a rule cannot be distinguished but it may be seen as a faint ring; when distinctly evident it takes a bluish tinge with hematoxylin. Although mitotic figures in such cells are seldom seen the above characteristics indicate a rapid proliferation. Not infrequently at the periphery of the lobule several of these newly-formed endothelial cells surround, in a ring-like manner, hyaline fragments of necrotic cells and simulate in appearance multinucleated cells into which, as will be shown later, many of the cells develop. Occasionally a stray leucocyte is seen in a necrotic cell. Phagocytic activity on the part of single cells within the necrotic focus is indicated by the occasional inclusion of a red blood corpuscle or fragments of necrotic liver cells. A very definite phagocytosis is also evident in the endothelial cells and especially in the Kupffer cells of the capillaries in the immediately adjacent normal liver. Here ten or twenty compressed and poorly staining blood corpuscles may be seen in a single endothelial cell. It is possible that some of these cells may have migrated from the spleen, where they are also very abundant, but the majority are definitely attached to the walls of the interlobular capillaries. In the endothelial cells definite mitotic figures, which can be readily distinguished from those in liver cells, are occasionally seen. They are, however, in proportion to the amount of proliferation, very few in number. Mitoses in liver cells are easily found, but always at a distance from the necrosis. They are never found in the vacuolated cells at the periphery, though between such the proliferation of endothelial cells is most active.

The picture of the third day is that of more advanced replacement of the necrotic cells by young endothelial and connective

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tissue cells. In many small areas these cells have more or less obscured the hyaline fragments of liver cells. Mitotic figures are more numerous in both liver and endothelial cells and for the first time are seen the large, pale oval or round liver cells described by Podwyssozki, Ponfick, and v. Meister. There is also evident an increase of chromatin in the nuclei of the liver cells. This occurs as a stippling due to numerous closely packed dots and granules which stain deeply and is suggestive of a premitotic activity.

During the fourth, fifth, sixth, and seventh days, the repair progresses with great rapidity but shows few new features. The bulk of the necrotic tissue is gradually replaced by the rapidly proliferating cells. Here and there, however, a few isolated necrotic hyaline masses, usually surrounded by very definite multinucleated cells of endothelial origin, may be seen. Mitotic figures in liver, endothelial and connective tissue cells are readily recognized; in the liver cells they are very abundant, three or four occurring sometimes in a single field of a high power lens. This rapid formation of liver cells occurs not only at the periphery but may, by the fourth day, be seen also in the midst of the destroyed area. Intercellular fibrillæ in the new tissue, first recognizable on the fourth day, rapidly increase and are very definite by the seventh day. Lymphoid cell infiltration first becomes prominent at this period and persists to a moderate extent in the later lesions. Such infiltration, however, is more abundant in the portal spaces, where there is also a proliferation of connective tissue, than in the repair about the necrotic areas. The leucocytic infiltration remains slight.

Despite the most careful study it has been impossible at this stage to determine anything definite concerning the proliferation of the small bile ducts. Not infrequently cells arranged in a circular or longitudinal manner and closely resembling newly-formed bile ducts have been seen. These have no relation to adjacent bile channels and no definite lumen. They closely resemble, however, the processes which Marchand described in yellow atrophy as arising from isolated groups of liver cells and assuming the appearance of pseudo-bile ducts. That they are such appears to be very probable, but absolute demonstration is lacking as it is not possible, even in serial sections, to differentiate in the closely packed mass of proliferating endothelial and

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connective tissue cells between them and other newly-formed structures. As will be shown later, however, the proliferation described by Marchand can be definitely demonstrated in the more advanced repair and it is possible that the ill-defined structures here described (fifth day) represent the earliest stages of this process.

Of the lesions beyond the seventh day, some on account of the small areas involved in the primary necrosis are unfortunately of little value in studying the intermediate stages of repair. In all, however, there is a very clear picture of the gradual transformation of the young granulation tissue into a very definite connective tissue and of the slow replacement of the latter tissue by newly-formed liver cells, but no new features are presented. In one (eleventh day) endothelial cells in which red blood cells are frequently seen are very numerous; in another (twenty-fifth day) lymphoid and plasma cells, usually present in but small numbers, are very abundant in and about the portal spaces.

The lesions of these intermediate stages, as well as the minute necroses of earlier periods, have been studied carefully to determine whether small areas of necrosis may be repaired by proliferation of liver cells alone without the formation of new connective tissue. Without going into detail it may be stated that such repair, except in minute areas involving but a few cells, has not been noted. In small areas the new formation of liver cells may be so abundant that the appearance may be that of simple hyperplasia of the parenchyma, but by careful study and the use of special stains a new formation of the supporting tissue above that necessary for simple restitution can always be determined. There is, on the other hand, very definite evidence, based upon a comparative study of late lesions of varying extent, that the superfluous connective tissue may be reduced to a minimum when the full development of the new liver cells is reached. Moreover, it can be definitely stated that in the smaller necroses a new formation of bile ducts does not occur; such proliferation takes place apparently only after the destruction of large areas of liver tissue.

The most advanced stage of repair occurring in this series was seen in an animal killed on the thirty-sixth day. The condition present, essentially a cirrhosis, may be described in a general way as a replacement of very extensive necrotic acreas by broad

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bands of very vascular connective tissue. In and about the new tissue important changes in the liver cells, as well as an excessive formation of new bile ducts, are seen. The liver cells outside of the zone of new tissue are compactly arranged, often irregular in shape and, at the extreme edge of the reactive process, even misshapen. The majority stain normally, but some are swollen and pale with a stippling of the nucleus. Mitotic figures may still be seen in such cells but they are widely scattered. Between these more nearly normal liver cells and the new fibrous tissue is a narrow margin in which fragments of necrotic liver cells still persist. Into this zone from the periphery project large multinucleated liver cells very irregular in shape. Similar cells, with oftentimes ten to fifteen deeply staining nuclei, surround fragments of necrotic cells. Some of these giant cells are in continuity with the strands of normal liver cells, while others are entirely isolated. Such cells may contain four or five hyaline particles which they apparently englobe and disintegrate. These multinucleated masses are essentially foreign body giant cells and though a few of the smaller cells are certainly of endothelial origin the majority appear to be altered liver cells. The protoplasm, which is large in amount, is characteristic of that of the liver cell in every way and, moreover, these cells not infrequently may be seen in direct continuity with strands of liver cells of normal appearance. Isolated giant cells of similar structure but without inclusions are also seen. The material enclosed is in greater part hyaline necrotic fragments of liver cells, but consists also, as determined by micro-chemical tests, of calcified material, occurring as smooth, almost colorless disks. Between these cells a fine connective tissue penetrates, but the great bulk of this zone is made up of giant cells. Similar cells are also seen in the midst of the denser fibrous tissue, sometimes occurring singly, but more frequently in connection with isolated islands of liver tissue.

A careful study of these cells leads to but one conclusion. They are altered liver cells which have developed as the result of an irregular type of nuclear division and which have acquired phagocytic powers which allow them to englobe and destroy necrotic material. There is a possibility that they may be formed by the fusion of several liver cells surrounding necrotic particles, but the occurrence of isolated multinucleated cells without inclu-

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sions indicate that such an explanation is not applicable to all these masses (see Fig. 3).

These cells are entirely different from the multinucleated structures formed by the advancing sprout of a new bile as described by Podwyssozki and have not, as far as I can determine, been previously described. McPhedran and MacCallum[18] in their account of the histology of acute yellow atrophy in man, picture somewhat similar structures, but in their description refer to them as cells of the bile ducts. They also describe both endothelial and hepatic cells containing inclusions, but not the multinucleated type of liver cell about necrotic fragments.

Proliferation of the bile ducts while most evident in the new tissue is seen also in the adjacent normal liver. In the latter location, from the canals of medium size, a solid process of newly-formed cells may not infrequently force its way between the normal liver cells and penetrate the zone of multinucleated cells. Oftentimes these strands, which are never canalized, show a division into terminal sprouts composed of conglomerate masses of cells resembling in a rough way giant cells.

Within the new connective tissue new bile ducts are very numerous. In serial sections these may sometimes be seen to have a connection with normal ducts, but more frequently they have no such connection and appear to be the results of the proliferation of persisting fragments of canals which had escaped the primary necrosis. For the most part they are solid processes with irregular swollen branchings or sprouts. Many of these budding processes have on cross section, as has been noted by Podwyssozki, the appearance of giant cells.

Those which have a distinct lumen are usually widely dilated and are either empty or contain a few leucocytes or desquamated cells. Such are usually irregular and tortuous with one or more solid branching processes. In form and structure the cells of which they are composed are intermediate between the true liver cell and the epithelium of the normal bile duct (see Fig. 4). They are usually irregular, or polyhedral in shape, though often oval but never cylindrical. They have a large amount of protoplasm which tends to stain lightly with eosin and closely resembles that of the liver cell. In the solid masses the protoplasm is not so evident. The nuclei are round or oval and, as a rule, vesicular. That these strucures are truly newly-formed is shown

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by the presence of mitotic figures which though not numerous may be found without great difficulty. In the older portions of the solid processes, as well as in the distinctly tubular structures, not infrequently may be found single cells much larger than the others and with protoplasm very similar to that of the fully developed liver cell. Similar cells of varying size may also be seen in the adjacent connective tissue either as isolated cells or, more rarely, attached to the new bile duct by a thin thread of protoplasm. Such pictures indicate conclusively that liver cells are formed from these structures. The formation of new liver cells from the terminal budding process I have not observed, though it is very probable, as Podwyssozki states, that they may eventually become isolated and be transformed into liver cells. At the stage here studied such transformation has, however, not been seen.

In addition to these processes, concerning the origin of which from preëxisting bile ducts there can be no question, other cell strands of very similar structure which are formed with equal certainty by a proliferation of liver cells are occasionally seen. These are always connected, with the normal liver substance at the periphery or with small islands of liver cells persisting in the center of the new tissue. They occur as closely massed double rows of cells or as groups of cells, usually with budding processes, but never canalized. The cells of which they are composed are similar to those of the solid processes arising from persisting bile ducts and from such processes they cannot be distinguished in their terminal portions; but upon tracing them to their origin they are found to be connected with true liver cells. The transition of the liver cells is gradual and all stages can be traced (see Fig. 3). The point of most abrupt change is usually at the narrowest part of the strand. That these structures may later become canalized is possible, but it seems more probable that they represent rapidly growing cells which later develop into typical liver cells. Such transformation, however, has not been observed. That these strands are not the result of compression of liver cells is shown by the fact that the most active growth is in the distal portion and in the midst, as a rule, of necrotic cells or newly-formed fibrous tissue. These structures are apparently very similar to those seen by Marchand in acute yellow atrophy of the liver.

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Summary.

In the necroses of the dog's liver, due to the injection of hemagglutinative sera, the first evidence of repair is the occurrence after thirty-eight hours of mitotic figures in the liver cells. At the end of the second day these have greatly increased and a considerable proliferation of endothelial cells has occurred in and about the necrotic areas. These last tend to encapsulate the necrotic cell fragments. From the third to the seventh day these processes advance, and with the formation of a young granulation tissue, the necrotic areas are largely replaced. While there is some evidence that areas of necrosis involving only a few cells may be repaired by proliferation of liver cells, without the formation of connective tissue, in all areas of appreciable size the latter is a prominent feature. Later, however, as the liver cells increase they replace the connective tissue to great extent. The coarser bands, however, remain. Throughout the entire process of repair the great power of the liver cells to increase by indirect division is the most striking feature. In the late stages of the repair of extensive necrosis many multinucleated liver cells, most of which surround fragments of necrotic cells, may be seen between the normal liver and the dense bands of new tissue. Here are seen also numerous giant liver cells without inclusions. New bile ducts formed from the uninjured larger ducts or from persisting fragments of the smaller canals, aid, by a transformation of their cells into liver cells, in the restitution of the liver parenchyma. The formation of new ducts and the transformation of their epithelium into liver cells occurs, however, only when large areas of liver substances are destroyed. Other cell strands, of the general appearance of new bile ducts, are formed to a slight extent by the direct proliferation of liver cells.

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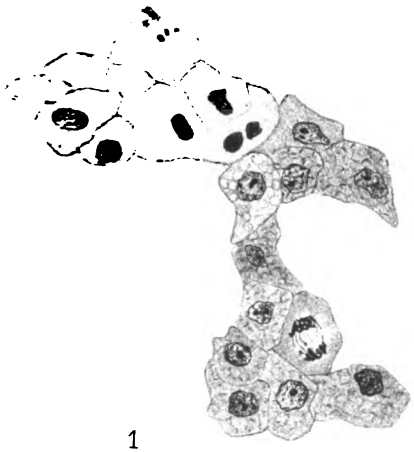
Plate II.



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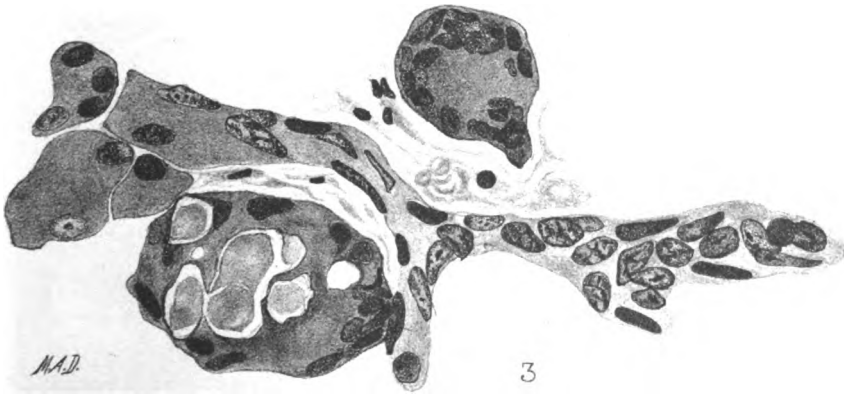

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EXPLANATION OF PLATE II.

FIG. 1. Mitotic figure in a liver cell in the neighborhood of a necrotic area. Thirty-eight hours. 4 oc., 1/12 obj., Leitz.

FIG. 2. Edge of necrotic area showing proliferation of endothelial cells and tendency of latter to encapsulate necrotic cell fragments. In the center is a necrotic cell containing a polymorphonuclear leucocyte. Sixty hours. 4 oc., 7 obj., Leitz.

FIG. 3. Solid process of cells formed by proliferation of liver cells and resembling a branching non-canalized newly-formed bile duct. Below is a multinucleated liver cell inclosing necrotic cell fragments; above is a similar giant cell without inclusions. Thirty-six days. 4 oc., 7 obj., Leitz.

FIG. 4. A newly-formed bile duct in which may be seen a mitotic figure and cells of a type intermediate between true liver cells and the epithelium of the normal bile duct. Thirty-six days. 4 oc., 1/12 obj., Leitz.

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LIVER NECROSIS AND VENOUS THROMBOSIS IN HORSES ACTIVELY IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXINS AND WITH STREPTOCOCCI AND THEIR PRODUCTS.*

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PLATE III.

Our search of the literature dealing with the anatomical and histological findings in man or animals dead of diphtheria, tetanus, or streptococcus infections, either natural or artificial, has failed to reveal to us definite records of the conditions similar to those which we are about to describe.†

Law in his extensive work on veterinary medicine gives no descriptions of liver necrosis in the horse exactly comparable to the condition in our series. However, from the statements in his chapter on "Hepatic Hemorrhage and Rupture" we gather the impression that various degenerations of liver cells and subsequent traumatic hemorrhage and rupture of the capsule are far more common in the horse than in man. From his pathological and clinical descriptions the usual cases of hemorrhage and rupture are undoubtedly much milder than those in our horses, as the latter rarely live over ten minutes after the onset of symptoms, while he gives five hours to five days as the period of duration.

Klitine[1] calls attention to fatty degenerations of the liver cells of guinea-pigs, the subjects of chronic experimental diphtheria. Dzierzowsky[2] also mentions the occurrence of fatty degeneration of the livers of horses which have been used in diphtheria antitoxin production.

*Read at the Sixth Annual Meeting of the American Association of Pathologists and Bacteriologists held at Baltimore May 18, 1906. Published in *Jour. Infect. Diseases*, 1906, iii, 619.

†That liver necroses have been frequently found in horses, the subjects of diphtheria antitoxin production, is no secret to many of those in charge of laboratories where such work is carried on, but no description of this condition has been published as far as we have been able to learn.

[1] *Arch. d. Sci. Biol.* (St. Petersburg), 1900, viii. 2.

[2] *Ibid.* 1902, ix. 293.

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Pettit and Girard[1] found complete necrosis of the spleen in a horse used in the production of antiplague serum.

We have to report the finding at autopsy of more or less diffuse necrosis of the liver, or thrombosis of some of the branches of the portal or splenic veins or of the pulmonary artery, either alone or in combination, in twelve horses. These animals had been subjected to repeated subcutaneous injections of the artificially produced toxins of the diphtheria or the tetanus bacillus, or of the various preparations of living or dead cultures, or of suspensions of dysentery bacilli or streptococci. In this series there are seven horses treated with diphtheria toxin, two with tetanus, two with streptococcus, and one with dysentery. A horse treated with diphtheria toxin and killed because of its crippled condition is added to the series for purposes of comparison, as its organs were found to be normal. (See Table 1.)

Superficial postmortem examinations were made of the first three diphtheria horses, and incomplete autopsies, in that no special search for thrombosis was made, on the second three horses in the series. (See Table 1.)

TABLE 1.

SHOWING AUTOPSY FINDINGS RELATING TO NECROSIS AND THROMBOSIS.*

Horse	Service.					Liver.		Thrombosis of Veins.		
	Disease.	Duration Yrs.	Duration Mos.	Sudden Death.	Killed.	Necrosis.	Rupture.	Liver.	Spleen.	Pulmonary Artery.
11....	Diphtheria	1	11	+		Diffuse	+	?	?	?
17....	"	2	1	+		"	+	?	?	?
28....	"	2		+		"	+	?	?	?
36....	Dysentery..		11	+		"	+	?	?	?
37....	Streptococcus	1	9	+		"	+	?	?	?
38....	"	1	9½	+		"	+	?	?	?
21....	Tetanus	3	3	+		"	+	+	+	—
29....	"	3	7	+		"	+	+	—	+
59....	Diphtheria		8		+†	—	—	+	—	—
57....	"		4		+†	—	—	—	—	+
43....	"	2	2	+		Diffuse	+	+	+	—
50....	"	1	7	+		Localized	—	—	—	—
56....	"	1	5		+†	—	—	—	—	—

[1] *Compt. rend de la Soc. de Biol.*, 1905, lviii. 272.

*The horses reported upon in this series include all those which have died, or have been killed, after a year and a half of service under the various treatments, since the observations were started.

†Horses 59 and 57 were killed because they were in such a disturbed state that it was impossible to control them. Horse 56 was hardly able to walk on account of the nearly immovable condition of the joints of its legs, and as its serum was of no value it was killed as a matter of economy. Its tissues were normal.

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As we have not been fortunate enough to be present when any of the horses died from the effects of hemorrhage and rupture of the liver, we are unable to give a detailed clinical picture of the symptoms preceding death in these cases. The general conditions as described by an attendant are as follows: The animals are apparently in their usual condition. They may have recently eaten a normal meal. Attention is first attracted to them by a rapid noisy breathing. The animal exhibits signs of collapse, and shortly falls to the floor. The breathing becomes very labored and the animal struggles. This stage is followed by a rapid and progressive loss of power, and death ensues. The whole course may not last over ten minutes.

At autopsy the peritoneal cavity contains a very large amount of fluid blood or serum and clots. The liver is usually very soft and friable, and is handled with difficulty. The capsule presents one or more ruptures, and at such places the liver substance is broken up into stringy fragments, interspersed with blood clots. (See Figure 1.)

Our attention was first called to the occurrence of thrombosis in association with diffuse necrosis of the liver by the findings at the autopsy of Horse 21, which occurred April 9, 1905. As is shown in Table 1, this animal had been in active service for the production of tetanus antitoxin for a period of over three years, and was in apparent excellent physical condition when she died in the manner already described. As the protocol of this animal gives a fairly representative picture of the conditions found in the other horses in the series, it will be given in full.

On opening the abdomen a large amount of bloody fluid escapes and many light red clots. The intestines are distended. The glands of the mesentery in the ileocolic region are enlarged and soft. The liver for the most part presents a yellowish-gray color; within the right lobe an encapsulated hemorrhagic mass. On section it is found that the entire liver is necrotic, presenting a grayish color and a consistence resembling that of thick oatmeal. In some places there is added to this the yellowish tinge of bile. The hemorrhage in the right lobe is found to be subcapsular and infiltrates the liver substance. It is essentially a hematoma beneath the capsule. No remnant of normal liver can be made out. Everywhere with slight pressure the liver substance can be removed leaving only the connective tissue framework.

The portal veins at their entrance to the liver are everywhere filled with smooth, firm, yellowish-white clots but slightly streaked with red. (See Fig. 2.) These clots project into all the smaller branches and are definitely adherent to the vessel wall. In most instances they completely

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Plate III.

To Illustrate Drs. Pease and Pearce's Article on "Liver Necrosis and Venous Thrombosis in Horses."

Albany Medical Annals, January, 1907.

Fig. 1.—Necrosis, Hemorrhage, and Rupture of Liver. Horse 43.

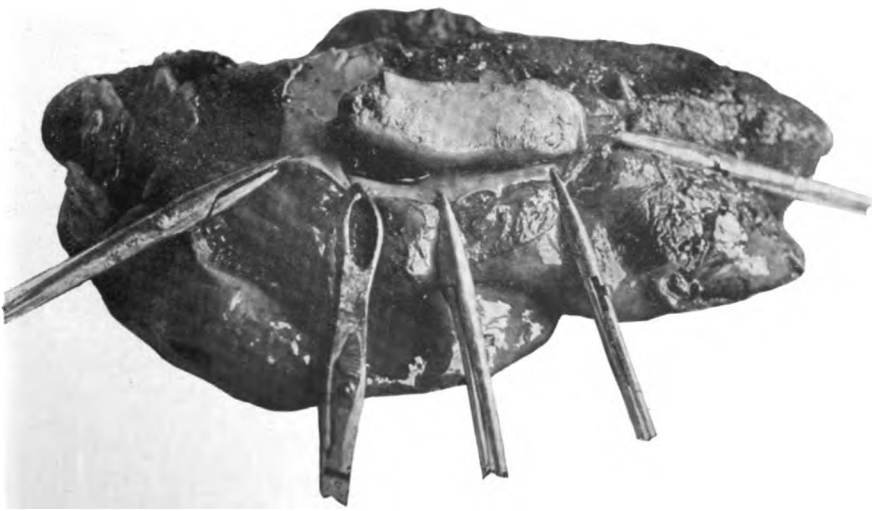

Fig. 2.—Thrombosis of Portal Vein. Horse 21.

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occlude the vessels in which they lie. On section through the liver small, firm, yellow, rigid clots protrude from the surface. The hepatic artery is free as are also the aorta and vena cava.

The spleen shows slight thickening of the capsule, and on section are found here and there a few soft swollen areas of a darker red than the surrounding tissue and in the center of each a clot similar to those found in the liver. On dissecting the main branch of the splenic vein an adherent thrombus can be followed for some distance. The splenic artery is free.

There is no accumulation of fluid in either pleural or pericardial cavity. The heart is pale, but otherwise negative. The lungs are pale and neither congested nor edematous. There are no thrombi in the pulmonary, coronary, or other vessels of the thorax. The kidneys are pale and cloudy. The adrenals are swollen and soft.

Careful examination of the vascular system shows no thrombi in vessels other than those of liver and spleen.

Anatomical diagnosis.—Widespread necrosis of liver. Hematoma of the liver. Focal hemorrhages in the spleen. Hemoperitoneum. Thrombosis of the portal and splenic veins.

Histology. Liver.—Sections taken at random from different portions of the liver show practically complete necrosis without leucocytic infiltration. Here and there the nuclei in small portions of a lobule may be distinguished, as may also those of the structures in the larger portal spaces, but otherwise the destruction is complete. Much bile pigment is present in the necrotic cells.

Sections passing through the periphery of the hematoma in the right lobe show this mass to be surrounded by a definite fibrous capsule from which prolongations pass into the adjacent necrotic tissue. In this fibrous tissue is a diffuse deposition of old blood pigment.

Other sections show loose granulation tissue penetrating and replacing the blood clot. Here and there in the older portions are newly formed bile ducts and liver cells, the latter being large, pale, and multinucleated.

Sections through five thrombi differing in size show a uniform structure —a definite network of fibrin enmeshing large numbers of leucocytes. At the periphery the fibrin is compact and hyalin, forming broad bands. Small bands of similar hyalin are found also in the other portions. Only an occasional red corpuscle is seen.

Spleen.—Section through the occluded vein shows a thrombus, similar in structure to those found in the liver and intimately adherent to the vessel wall, which is greatly thinned and infiltrated with lymphoid cells. In the tissues about the vessels a diffuse hemorrhage has occurred. Elsewhere the spleen is normal.

Lymph nodes.—The sinuses are dilated and closely packed with large, pale, endothelial cells. These are but slightly phagocytic. In the lymph nodes are many plasma cells, with, however, no diminution of the lymphoid cells. Throughout the lymphoid tissue is an abundant deposition of old blood pigment.

Adrenal.—Normal.

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Lung.—Congestion, moderate edema in focal areas and slight thickening of walls of alveoli.

Kidney.—Cloudy swelling of epithelium of tubules, few foci of lymproid cell infiltration.

Heart muscle.—Cloudy swelling.

Histological diagnosis.—Necrosis of liver with repair about hematoma. Mixed thrombi of portal vessels. Thrombosis of splenic veins with perivascular hemorrhage. Endothelial hyperplasia of lymph nodes with deposition of old blood pigment. Congestion and edema of lung. Cloudy swelling of heart and kidney.

Abstracts from Clinical Histories and Protocol.

Horse 11.—*Clinical notes.*—Horse about 10 years old. Used in the diphtheria service. Had stiff leg joints at time of entering, which gradually became worse until horse was almost constantly confined to its stall.

The maximum antitoxin strength of its serum was approximately 500 units per c.c. During the last six months of its life the horse showed progressive emaciation. After a year and 11 months of treatment the horse suddenly developed the usual symptoms of hepatic rupture, and died in a few minutes.

Autopsy notes.—A superficial examination shows diffuse necrosis and hemorrhage of the liver, with rupture of the capsule and consequent hemoperitoneum.

Horse 17.—*Clinical notes.*—Sound horse of uncertain age. Diphtheria service. Always remained well and active during period of treatment of two years and one month. Antitoxic strength of serum varied from 200 to 400 units per c.c.

The animal retained its usual weight until death, which occurred suddenly after the development of the usual symptoms of hepatic rupture.

Autopsy notes.—Examination incomplete. Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum.

Horse 28.—*Clinical notes.*—Sound horse about 12 years old. Diphtheria service. Active during entire period of treatment of two years. Maximum antitoxic strength of serum 400 units per c.c. Gradual loss of flesh during last two months of life. Had frequent abscesses at the sites of injection with accompanying high temperatures. Died during the night.

Autopsy notes.—Examination incomplete. Diffuse necrosis of the liver, with hemorrhage, rupture, and hemoperitoneum.

Horse 36.—*Clinical notes.*—Sound horse about 10 years of age. Dysentery service. Progressively increasing doses of autolyzed suspensions of surface growth of agar cultures of two strains of *B. dysenteriae* were injected alternately into this horse. They produced very severe reactions, during which the temperature would often rise to 104° F., or over, and the site of the injection would become very much swollen and painful, and the animal would refuse to eat for several days.

After a total of 496 c.c. of these autolyzed suspensions of dysentery bacilli had been administered, living broth cultures of the same strains were administered. They caused much less vigorous systematic reactions.

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About seven weeks before death the animal developed a severe diarrhea, which was checked with difficulty. It also began to lose weight, and finally became much emaciated. The animal was found dead early in the morning.

Autopsy notes.—Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum. Other organs, including intestinal mucous membrane, normal microscopically. Cultures from the usual organs were negative. No thrombosis was noted in any of the vessels of the liver, spleen, or lungs, but attention was not directed particularly toward this point.

Histological diagnosis.—Intense diffuse granular degeneration with irregular focal areas of necrosis in the liver.

HORSE 37.—*Clinical notes.*—Sound, active horse of about 12 years of age. Streptococcus service. Received, in gradually increased doses, a total of about three and a half liters of autolyzed salt solution suspensions of a rabbit-virulent streptococcus, grown on the surface of large agar plates, and later about half a liter of broth cultures of the same streptococcus. Small subcutaneous abscesses followed the later injections. The animal retained its weight and activity during the treatment. It was found dead one morning.

Autopsy notes.—Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum.

HORSE 38.—*Clinical notes.*—Streptococcus service. Age uncertain, but animal appeared to be at least 20 years old. Had somewhat crippled legs. Became emaciated during the last two months of life. The treatment was the same as was given Horse 37 and was started at the same time, except that another streptococcus was used. This animal also died during the night, about two weeks after the death of Horse 37, and the autopsy findings were in general the same as those of that animal.

HORSE 21.—*Clinical notes.*—Sound active mare about 16 years old. Tetanus service. Always well. Remained active and retained its weight during life. She died in the manner already described. (Full protocol will be found in the text.)

HORSE 29.—*Clinical notes.*—Sound active horse about 10 years of age. Tetanus service. Remained well until about two months before death, when it had frequent rises of temperature and difficulty of breathing which were directly due to the toxin injections. During the last half-year had frequent acute abscesses at sites of injection. This horse died in the manner already described.

Autopsy notes, anatomical diagnosis.—Diffuse necrosis of the liver with subcapsular hemorrhages and rupture. Hemoperitoneum. Multiple thrombi of portal veins. Multiple thrombi of pulmonary arteries. Multiple infarcts of the lungs. General lymphatic hyperplasia.

Histological diagnosis.—Necrosis, congestion, and hemorrhage of the liver. Thrombosis of portal veins and pulmonary arteries. Focal edema and congestion of the lungs with slight leucocytic exudate. Acute endothelial hyperplasia of the lymph nodes. Congestion of the spleen. Acute interstitial (non-suppurative) nephritis. Tests of liver and kidneys for amyloid changes were negative.

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HORSE 59.—*Clinical notes.*—Diphtheria service. Sound active horse about 10 years old. After eight months of treatment was taken suddenly while in the paddock with difficulty of breathing and evident distress. Respiration became very rapid and labored, and at the same time there was very marked spasmodic tenesmus, but no dung was passed. Pulse rate about 90. The horse became weaker as the above condition continued, and finally was unable to stand, and when down struggled violently, so that it became necessary to kill him about five hours after the onset of the symptoms. The maximum antitoxic strength of the serum was 300 units. The last bleeding occurred about 10 days prior to death.

Autopsy notes, anatomical diagnosis.—Thrombosis of portal veins. Focal hemorrhages of liver and spleen.

Histological diagnosis.—Granular degeneration and focal hemorrhages of liver. Leucocytosis.

HORSE 57.—*Clinical notes.*—Diphtheria service. Sound horse 10 years old. This animal had lived under the same conditions as the other horses in the service for 10 months before the treatment was begun. The toxin injections were pushed with considerable vigor, so that during the four months of treatment he received 14 injections, and had an average of nearly 3.9 days of temperature over 101° F. for each injection given, which is the maximum for any of the horses in this series. The animal appeared to stand them satisfactorily, and gave a serum of 300 units per c.c. at the second bleeding. Immediately after the third withdrawal of eight liters of blood the animal suddenly fell to the floor in a state of collapse. Nothing was thought of this, as it is not an uncommon occurrence when larger amounts of blood are withdrawn. The horse did not attempt to rise later on, and all efforts to stimulate the animal with strychnin, etc., and to support him in slings, were futile. That night and the following day he struggled violently, and could not be quieted with full doses of morphine or chloral. The next night, and also part of the following day, he rested comfortably. Later he again became violent, and as the temperature rose to 106, and as it seemed impossible to control him, he was killed in the evening. His head and shoulders were badly bruised, and as the autopsy was not performed until the next morning, the tissues and organs showed a well-developed gas bacillus infection at that time.

Autopsy notes, anatomical diagnosis.—Acute endarteritis and thrombus formation in the main trunk of the pulmonary artery. Thrombosis of intrapulmonary branch of left pulmonary artery. Atalectasis of portion of left lung. Hemorrhagic infarct of left lung. Cloudy swelling of the myocardium. Fatty transformation of the liver with evidences of gas bacillus infection. No hemorrhage or other evidence of antemortem necrosis was apparent.

Histology.—Complete postmortem decomposition with gas blebs in the liver and lungs. Tests for amyloid changes in all organs were negative.

HORSE 43.—*Clinical notes.*—Diphtheria service. Sound horse about 10 years old. Remained well and active during treatment for two years and two months. During the last few months of life was subject to abscess formation at sites of injection. Its serum showed 500 units per c. c. after

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three months of treatment, and varied from that point to 700 units during the next year, after which time it varied from 300 to 500 units, until three months before death it dropped suddenly to below 200 units. Death occurred in the manner already described.

Autopsy notes, anatomical diagnosis.—Extensive necrosis of the liver with multiple hemorrhages. (See Fig. 1.) Thrombosis of small branch of the portal vein in the right lobe. Rupture of encapsulated hemorrhages in the peritoneum. Hemoperitoneum. Thrombosis of the splenic veins. Hemorrhage and edema of gastrohepatic lymph nodes. Chronic peritonitis.

Histological diagnosis.—Necrosis and amyloid degeneration of the liver, with moderate regeneration. Chronic hemorrhagic cysts of the liver. Organizing thrombi of portal and splenic veins. Amyloid degeneration of Malpighian bodies of spleen. Proliferation of intima of splenic arteries. Hemorrhage and endothelial hyperplasia of gastrohepatic lymph nodes.

HORSE 50.—*Clinical notes.*—Diphtheria service. Horse of uncertain age, of good condition on entering. Gradually became almost helpless through stiffness of joints and blindness. Had frequent abscess formations at sites of injections. Antitoxic strength of serum never over 300 units c.c., and usually from 200 to 250 units. Was found dead one morning, and stall showed evidences of continued struggling. The front of the stall was covered with frothy mucus. The coughing up of this material has never been observed in the horses dying from rupture of the liver.

Autopsy notes, anatomical diagnosis.—Necrosis and hemorrhage of left lobe of the liver. Congestion of lungs and the right lobe of the liver. General lymphatic hyperplasia. Abscess of subcutaneous tissues of back. Cloudy swelling of heart and kidneys. Acute endarteritis of left renal artery. Thickening of intima of splenic artery. Focal lesions of adrenals. Chronic peritonitis.

Histological diagnosis.—Congestion, edema, hemorrhage, amyloid degeneration, and necrosis of the liver. Chronic interstitial myocarditis. Subpericardial hemorrhage with hyalin degeneration of muscle fibers, and leucocytic infiltration. Edema and congestion of lungs with hemorrhages. Edema and hemorrhages of lymph nodes. Amyloid transformation of Malpighian bodies of the spleen. Localized endarteritis and mesarteritis of left renal artery.

HORSE 56.—*Clinical notes.*—Diphtheria service. Horse about nine years old on entering. Developed stiffness of joints and became badly crippled. Antitoxic strength of its serum was rarely up to 300 units per c.c., and usually showed but 200 units. After a year and five months of treatment the animal was killed.

Autopsy notes.—Macroscopically and microscopically the liver, spleen, kidney, pancreas, adrenals, lymph nodes, lungs, and heart muscle appeared to be normal.

Table 1 presents a summary of the findings relating to necrosis of the liver and thrombosis in twelve horses which have presented such changes, and also gives those of one horse in whom all the organs were normal, although it had been subjected to active

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treatment with diphtheria toxin for a period of a year and five months. The other changes found in the tissues of these twelve horses varied to some extent, but such changes did not differ greatly from those to be found in the tissues of fatal cases of diphtheria in man, such as endothelial hyperplasia of lymph nodes, and cloudy swelling of kidney epithelium and heart muscle, etc.

One or two unusual findings were, however, observed. In Horses 43 and 50, belonging to the diphtheria service, amyloid changes were observed in both liver and spleen, and especially in the latter, but were not present in the kidney, heart muscle, or lymph nodes. These animals had developed an unusual number of subcutaneous abscesses at the sites of the toxin injections during the later months of their lives.

In the liver in tetanus horse 21 around the margin of a subcapsular hematoma, and in the necrotic liver of diphtheria horse 43 about the larger portal spaces were found evidences of attempted regeneration in the way of newly formed false bile ducts, and, especially in the latter horse, of columns of newly formed liver cells. In the necrotic livers of the other horses there were no evidences of repair. Also in the tetanus horse 29 there were evidences of beginning interstitial nephritis, of the acute non-suppurative type found in diphtheria of man, accompanying widespread disintegration of the epithelium of convoluted tubules.

A study of Table 1 will show that horses presenting necrosis of the liver did not, in all cases, show thrombosis in any organ, nor in animals presenting both conditions was the thrombosis in the hepatic veins always as extensive in its distribution as the necrosis. On the other hand, two diphtheria horses presented thrombosis without evidences of liver necrosis. Unless, therefore, the thrombosis in some instances is secondary and dependent upon the necrosis, and in other cases upon other conditions, we cannot attach much significance to their fairly close association.

That the necrosis is not usually of sudden or rapid development is shown by the fact that the livers of two horses, tetanus horse 21 and diphtheria horse 43, presented encapsulated hematomas of various sizes scattered throughout the liver substance. The thickness of the capsules and the character of their contents indicated their formation at least several months prior to death,

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which in turn demonstrated the still earlier existence of extensive necrosis.

With the object of ascertaining whether there existed any common factor in the clinical histories of these horses which might assist in arriving at either the etiology of the liver necrosis or the thrombosis, or of both, the individual factors in the history of each horse which has died since these conditions were noted, have been worked out and are compared in Tables 1, 2, 3 and 4.

It is evident from the fact that some horses in the diphtheria, tetanus, streptococcus, and dysentery services presented diffuse necrosis of the liver, that this condition is not due to any special pathogenic property of any one of the organisms used in the immunizations. If, however, it is the result of the activity of some bacterial property, it is not necessary to suppose that the agent in all cases belongs to either the soluble toxins or the so-called bacterial endotoxins, for the reason that the tetanus horses received only toxin which had been filtered through Pasteur-Chamberlain filters, and consequently no bacterial bodies were injected; and, on the other hand, the streptococcus horses which received large amounts of dead cultures were equally affected.

It hardly seems probable that any of the constituents of the various media used in the preparation of the toxins and toxic products, such as the meat extractives, peptone, etc., could be the causative agent of the liver necrosis, for the reason that the two horses of the streptococcus service (37 and 38) received only about 500 c.c. of broth containing such materials during a period of about one and three-quarters years, the other later injections consisting of suspensions of bacteria or their bodies in physiological salt solution. (See Table 2.)

Neither can any effect produced by the repeated abstraction of blood from such horses be the main cause of the liver necrosis, for, as is seen in Table 2, Horse 36 in the dysentery service was bled only one liter on a single occasion, and the streptococcus horses 37 and 38 had bled eight liters, abstracted on only six and seven occasions respectively during a period of a year and three-quarters. On the other hand, Horse 56 of the diphtheria service was bled eight liters on 18 occasions during a period of a year and a half, and at death its liver was absolutely normal.

It is likewise possible to exclude the antiseptics used in the preservation of the bacterial toxic agents as an important factor in the production of liver necrosis, although nearly all the toxic

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materials administered contained from 0.3 to 0.5 per cent of either carbolic acid or trikresol. A study of Table 2 will show that the actual amounts of these antiseptics received by the different horses varied from about 2.5 c.c. during 11 months in the case of dysentery horse 36, and about 17 and 19 c.c. in the streptococcus horses 37 and 38 respectively, to 165 and 235 c.c. in the tetanus horses 21 and 29 respectively, and from 190 to 385 c.c. in the various diphtheria horses presenting necrosis of the liver. In other words, the horses receiving the larger amounts of antiseptics lived the longer periods.

Nor could we explain the necrosis of the liver by any general disturbance of metabolism due to the injections of the bacterial

TABLE 2.

SHOWING RELATION OF THE MATERIALS INJECTED AND OF REPEATED BLEEDINGS TO LIVER NECROSIS.

HORSE.	Toxic Broth Injected.	Autolyzed or Dead Bacterial Suspensions.	Amount Carbolic Acid Injected.	Number of Bleedings (8 Liters Each).	Condition at Death.	Extent of Necrosis.
11	42 liters		210± c.c.	21	Poor	Extensive.
17	59 "		295±	25	Good	"
28	38 "		190±	20	Poor	"
36		800 c. c.	2½±	0	"	"
37		4 liters	17±	6	Good	"
38		4½ "	19±	7	Poor	"
21	63 liters		165±	29	Good	"
29	78 "		235±	35	"	"
43	77 "		385±	25	"	"
50	50 "		250±	18	Poor	Left lobe.
56	33 "		165±	18	"	No necrosis

toxic agents, for some of the animals which showed the most diffuse necrosis were to all outward appearances and according to their weight in excellent physical condition, as is indicated in Table 2.

There is also no apparent reason for believing that the conditions under which such horses are kept in antitoxin stables is the main factor in the causation of the necrosis. Diphtheria horse 56 was kept under the same conditions as the others for a period of a year and a half, and at autopsy the liver was normal.

A careful study of the temperature charts and a knowledge of the manner in which the horses withstood the injections will, perhaps, give as likely an explanation of the causation of the necrosis as can be found. In Table 3 will be found the number of days during the treatment of each horse, in which the temperature

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stood at the various points from 101° to 105°+ Fahrenheit. It will be seen that a fair degree of uniformity exists in this number of days of fever in the animals which had necrosis of the liver. These increases of temperature cannot be accepted, however, as an exact index of the character of the reaction, as some horses commonly have considerable fever without any other manifestation of serious disturbance after toxin injections. However, the variations in the temperature curves are due largely to the type of immunization. Thus the dysentery horse had apparently fewer days of temperature than those used in the diphtheria work, but he lived under the treatment only about one-half as long as the latter. It is well known that horses are particularly

TABLE 3.

SHOWING RELATION OF REACTIONS DUE TO TOXINS INJECTED TO LIVER NECROSIS.

HORSE.	Disease.	Duration of Treatment.		Number Injections.	DAYS OF TEMP. OVER 101° FAHR.					Average Days of Temperature for each Injection.
					101 to 102	102 to 103	103 to 104	104 to 105	Total.	
		Yrs.	Mos.							
11.....	Diphtheria	1	11	75	95	73	14	1	183	2.4
17.....	"	2	1	77	85	75	22	2	184	2.4
28.....		2		69	92	74	38	9	213	3.1
36.....	Dysentery		11	46	86	62	14	4	166	3.6
37.....	Streptococcus	1	9	54	76	44	19	2	141	2.6
38.....	"	1	9½	60	98	48	5	1	152	2.5
21.....	Tetanus	3	3	126	95	69	9	1	174	1.4
29.....	"	3	7	138	135	53	8	2	198	1.4
43.....	Diphtheria	2	2	77	92	65	31	3	191	2.2
50.....	"	1	7	64	79	39	20	0	138	2.1
56*.....	"	1	5	59	63	57	34	2	146	2.4

susceptible to injections of cultures of true or paradysentery bacilli; and this horse withstood the injections very poorly. On the other hand, the horses treated with injections of even large doses of tetanus toxin show only slight disturbances, and in harmony with this is the long duration of the period of treatment in horses 21 and 29, each of which lived considerably over three years. The two streptococcus horses withstood the injections about as well as the diphtheria animals. Each lived approximately a year and three-quarters, and that was nearly the average life, a year and eleven months, of the five diphtheria horses.

As the horses used in each service lived approximately the

*No liver necrosis in this horse.

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same length of time under their respective treatments, and as the animals receiving the injections of the toxins causing the milder reactions lived for considerably longer periods than did those receiving toxins producing the most violent reactions, and as we have excluded other possible factors, we are led to the conclusion that the liver necrosis is, without much doubt, mainly the effect of the administration of repeated doses of the bacterial products.

That some of the other factors which appear to be excluded by our findings may be contributory to the main causative agent in some instances cannot be denied.

A possible relationship between the effect of the toxic products of these bacteria on the liver cells and the production of antitoxic or other anti-bodies is not capable of either positive or negative determination from the available data.

In the diphtheria and tetanus horses under consideration no relationship can be made out between the course of the necrotic changes in the liver and the well-known progressive decrease in the antitoxic strength of the sera of some horses after prolonged treatment. Thus diphtheria horse 50, which had necrosis of the liver, gave an antitoxin of from 300 to 350 units per cubic centimeter in only two early bleedings out of a total of 15, the others producing sera of from 200 to 250 units. On the other hand Horse 56, which showed a normal liver when killed after an immunization life of one year and five months, gave almost identically the same grades of serum in seventeen bleedings. That is, the early bleedings gave sera of 400 units, and those subsequently from 300 down to 200 units, which was the strength at the time the animal was killed. These findings would seem to indicate that the customary decrease in antitoxic power, which occurs in the sera of many horses as their immunization proceeds after the first few months, is not exclusively due to a progressive liver necrosis. However, the amount of data obtained does not permit us to draw any conclusions concerning the possible relation of the liver to antitoxin production. The bleedings are too infrequent, and the continuation of the antitoxic power of the serum is probably dependent upon so many factors that the absence of liver necrosis in one horse whose serum had shown the usual progressive loss of power, is entirely insufficient evidence to warrant the exclusion of the liver as a factor in antitoxin production.

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Brunton and Bokenham[1] have endeavored to show that the liver is capable of producing diphtheria antitoxin by the action of toxin passed through the portal venous system. While it might be questioned whether they have clearly proven the formation of true antitoxin, they undoubtedly showed that the liver cells have an affinity for pure diphtheria toxin, and are capable of at least greatly reducing the poisonous power of the crude product.

A similar affinity of the liver cells of some invertebrates for tetanus toxin has been claimed by Metchnikoff.[2] He states that in scorpions injected with tetanus toxin the liver is the only organ which absorbs and retains the toxin.

If the liver is capable of absorbing large amounts of the toxic bacterial products, and if their direct action on it is the means of producing liver necrosis, then in most horses treated with such agents the liver is very probably capable of disposing of large amounts of these products without injury; for the liver necrosis is not present in many horses, at least, which have come to autopsy after injections of considerable amounts of diphtheria toxin distributed over several months. (See history of Horse 56.)

In view of recent work on autolysis of liver tissues *in vitro*, it may not be out of place to consider the possibility that this late necrosis is due to alterations or disturbances of those factors which prevent the action of the autolytic ferments normally present in the liver.

Baer and Loeb[3] have shown that weak alkalis retard and weak acids stimulate the autolytic ferments in the liver, and that the elements in normal serum which strongly retard or prevent autolysis are the serum albumin and the fibrinogen, while the serum globulin has the opposite effect, namely, a strong stimulating action on the autolytic ferment.

Hiss and Atkinson,[4] Butjagin,[5] and others claim that an increase in the globulin content of the blood occurs during active immunization, although this is disputed by Müller.[6]

Butjagin also demonstrated a gradual decline in the alkalinity of the blood during the later part of the period of immunization.

[1] *Jour. Path. and Bact.*, 1904, x, 50.
[2] *L'Immunité*, etc., Paris, 1901, p. 343.
[3] *Arch. f. exper. Path. u. Phar.*, 1905, liii, 1.
[4] *Jour. Exper. Med.*, 1900, v, 47.
[5] *Hyg. Rund.*, 1902, xii, 1193.
[6] *Beiträge z. chem. Physiol. u. Path.*, 1905, vi, 454.

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In view of the work of Baer and Loeb, the occurrence of these or other similar blood changes may have some relations to the development of the liver necrosis or autolysis.

Thrombosis.

Of the horses upon which careful autopsies were performed and which presented necroses of the liver, extensive coexisting thrombosis of the veins of that organ was found in one (Horse 21), and to a lesser extent in two others (29 and 43). In the horses treated with streptococcal and dysenteric bacterial products, no careful searches of the entire substance of their livers with this point in view were made.

In one diphtheria (43) and in one tetanus (21) horse the veins of the spleen were likewise the seat of thrombosis to a greater or less extent. The other tetanus horse (29) had extensive thrombosis of the pulmonary arteries and infarction of the lungs.

As has been stated, two diphtheria horses had thrombosis occurring without necrotic changes in the liver. In one (59) the thrombosis was confined to three large branches of the portal vein in the liver, while in the other (57) the thrombosis was present in the main branch of the pulmonary artery and in the intrapulmonary branch of the left pulmonary artery. In the latter horse the clinical manifestations arose immediately after a withdrawal of the usual eight liters of blood, and may have been due to the formation of a blood clot at the site of this operation and the detachment and passage of the clot into the venous circulation. The thrombus in the main pulmonary artery was in the form of a pedunculated vegetation about the size of a walnut. The horse apparently suffered considerable thoracic pain, and was so weak as to be unable to stand even with the assistance of slings.

The other horse (59) with localized thrombosis of the portal veins gave indications of great pain in the abdominal cavity, with tenesmus, and also complete prostration and excessively rapid respiration and a high pulse rate. After the continuation of these symptoms for about five hours the animal was killed, and the autopsy performed immediately.

If the conditions operating to produce the thrombosis in this case are the same as in those where the thrombosis coexisted with liver necrosis, it is remarkable that it should have occurred as early as the eighth month of the immunization period, and

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that the clinical symptoms should be so much more severe than in those cases where thrombosis occurred later and more extensively.

In looking for some factor or condition operative during the period of treatment which might be considered as of etiological significance for the thrombosis, we are not afforded as much data as we would like, owing to the failure to examine and note particularly the presence or absence of thrombi in the first few animals which died from rupture of the liver with hemorrhage. Thus we have no definite information on this point in three diphtheria, one dysentery, and two streptococcus horses.

From the data tabulated in Table 4 it can be seen that by excluding the horses with early thrombosis the treatment given and its effects on the three remaining horses are quite similar. The

TABLE 4.

RELATION OF THE TREATMENT OF HORSES TO THE DEVELOPMENT OF THROMBOSIS.

NUMBER.	Diseases.	Immunisation Period.	Liters of Broth Injected.	Amount of Carbolic Acid Injected.	Days of Tem. over 101°	Number Bleedings of 8 Liters Each.
59.....	Diphtheria	8 mos.	16½	82± c.c.	91	7
57.....	"	4 "	5½	27±	54	43
21.....	Tetanus	3 yrs. 3 "	63	165±	174	29
29.....	"	3 " 7 "	78	235±	198	53
43.....	Diphtheria	2 " 2 "	77	385±	191	25

only exception is to be found in a considerable difference in the amounts of carbolic acid or trikresol which the horses received with the toxins injected. We are of the opinion that these antiseptics played no essential part in the production of the conditions favoring thrombosis.

We cannot, however, readily exclude in this way a possible influence favoring thrombosis by the injection of those elements which make up the broth used for toxin production, such as peptone, meat extractives, etc. Likewise we cannot exclude the effects of the repeated abstraction of eight liters of blood every three or four weeks. We are unable, therefore, by any process of exclusion to form any definite opinion of the part played in the thrombosis by the pathogenic activity of the bacterial toxins injected into these horses.

If, however, we ascribe to the early thromboses the same etiological conditions as bring about the late thromboses, then we

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can find no common factor in the treatment of our horses which might have been operative in the determination of this condition.

There are, however, some noteworthy features in the relation of thrombosis to the liver necrosis in some of the horses.

Thus in Horse 50, which was the only animal with necrosis of the liver which was thoroughly examined for thrombi and none found, the necrosis and hemorrhage of the liver was not general but localized almost exclusively in the left lobe, and was evidently not so far advanced as in the other animals. As the autopsy also revealed myocarditis with small subpericardial hemorrhages, and amyloid degeneration of the liver and spleen, local endarteritis, edema, and congestion of the lungs with small hemorrhages, it is not unlikely that the animal did not die from the effects of the liver necrosis, especially as there was no rupture of that organ. It is not improbable, therefore, that thrombosis would also have occurred in this horse if he had lived longer.

In Horse 29 the portal veins in which thrombi were found corresponded closely with the areas of necrosis in the liver, and it was noted that the thrombosis seemed to proceed from the smaller veins outward into the larger branches, ending there in large, round-ended clots.

In Horse 43 the extensively necrotic liver showed thrombosis only in one small portion of the right lobe, but considerable thrombosis occurred in the spleen.

Thus, taking the findings as a whole, it can be stated that while all necrotic areas in the liver did not have coexisting thrombosis, there were no thrombi in the portal veins other than in the necrotic portions, except in the two horses already described which died with early thrombosis without necrosis. It is possible, therefore, that in some animals, at least, the portal thrombosis may be caused by lesions of the vessel walls secondary to the liver necrosis.

It is the opinion of Smith[1] that the pathological effects of the periodic losses of blood in antitoxin horses lead in certain cases to serious derangements and death. He shows that in many horses which have been bled five liters every three or four weeks for periods of from nine months to over four years, the red blood corpuscles have a reduced osmotic tension. He believes that this condition is due to the repeated bleedings and not to the toxin injections.

[1] *Jour. Med. Res.* 1904, xii, 385.

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In Pettit and Girard's case of necrosis of the spleen in an anti-plague horse, the authors express the qualified opinion that the necrosis was not due to the periodic bleedings.

In so far as necrosis of the liver is concerned, our data do not warrant the conclusion that the periodic bleedings have any special etiological relation to it. If, therefore, the lowered osmotic tension is due to the repeated losses of blood, it is not probable that such lowered tension is in any way responsible for the liver necrosis. Whether it is or is not a factor in the causation of the thrombosis we are not prepared to state.

Butjagin has shown the presence of this phenomenon and also the existence of such alterations in the blood serum as an increase in the specific gravity, changes in albumin and globulin content, electrical conductivity, alkalinity, and refractive index during the immunizing process.

Similar work on one or more of these aspects of the subject has been reported by Müller[1] and others.

What relation exists between these alterations in the morphological, chemical, and physical conditions of the blood constituents and the pathological conditions noted by us, remains to be solved.

Summary.

In a series of twelve horses, actively immunized with the products of certain pathogenic microorganisms, autopsies revealed widespread liver necrosis in nine, and localized liver necrosis in one.

Thrombosis of the portal veins was present in three, of the splenic vein in two, and of branches of the pulmonary artery in one, of the nine horses showing widespread necrosis. One horse had thrombosis of branches of the portal veins and another of the pulmonary artery without liver necrosis. Six horses were not carefully examined for thrombosis.

The evidence obtained tends to exclude the materials such as peptone, beef extractives, and antiseptics, such as carbolic acid, injected with the toxins, and also the repeated bleedings practiced, from any important rôle in the production of the liver necrosis. On the other hand, the evidence leads to the conclusion that the toxic bacterial products injected are directly or indirectly responsible for the production of this pathological condition.

[1] *Loc. cit.*

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The evidence is not sufficient to determine which, if any, of these factors is responsible for the occurrence of the venous thrombosis. A possible etiological action by the antiseptics injected is excluded. In some cases the portal thrombosis may result from the liver necrosis.

NOTE.—Since this paper went to press another horse (No. 60) has died after a year and four months of treatment. During the first four months of this period it received diphtheria toxin, and after that until death small doses of tetanus toxin. The horse had a very slightly varying temperature of from 104° to 106° during the two weeks prior to death, and gradually became weaker during the last few days of life, and died during the night. Just prior to the onset of the high temperature an edematous condition of the genital sheath developed, followed by a tremendous increase in the size of the penis, apparently due to venous stasis. Later the use of the left hind leg became impaired.

At autopsy thrombosis of the left iliac vein, the inferior vena cava, the veins of the tissues about the penis, the splenic vein outside the spleen, the portal vein, and some of its branches in the liver, and of some of the pulmonary arteries was found. There was no evidence of necrosis in the liver. There was a general hyperplasia of the lymph nodes.

AFFECTIONS OF THE THYROID GLAND:

A CLINICAL AND PATHOLOGICAL STUDY.*

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PLATES IV, V, AND VI.

During the past few years as a result of the great advances in surgery of the thyroid gland, the study of the many diseases of this organ has been placed upon an intelligent clinical and pathologic basis. There still remains, however, a lack of uniformity not only in the classification of the various lesions but also in the interpretation of their etiology and their pathologic significance. It was with the object of adding, if possible, to our orderly knowledge of the pathology of the thyroid that this study of a large series of cases was undertaken.

Material.—Since the opening of the Bender Laboratory, in 1896, a period of about ten years, material removed at operation from sixty-one cases of thyroid disease has been examined. It

*Read before the Medical Society of the County of Albany, February 14, 1906. Published in the *Annals of Surgery*, 1906, xliii, 805.

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is upon this material, mainly from the surgical clinic of the Albany Hospital, together with three of my own cases, that this present study is based. Including, as it does, examples of all of the more important affections of the thyroid gland, with careful gross and microscopic descriptions, this group of cases offers unusual opportunities for investigation.

This material may be classified as follows:[1]

Class.	Disease.	No. of Cases.
I.	Simple hypertrophy	26
II.	Adenoma	9
III.	Recurrent adenoma	3
IV.	Cyst	12
V.	Metastatic thyroid tumor	1
VI.	Exophthalmic hypertrophy	6
VII.	Chronic thyroiditis	1
VIII.	Tuberculosis	2
IX.	Carcinoma	1

These lesions fall naturally into three groups,—the hypertrophies, the tumors, and the inflammations,—and should perhaps more properly be discussed in this order. Several departures, however, will be made in order to more clearly present the relations of the various lesions. Simple hypertrophy and adenoma as they possess, histologically, much in common, will be considered in sequence, thus affording a better opportunity for differentiation. The exophthalmic type, aside from the fact that it represents a diffuse process, bears no points of resemblance either clinically or pathologically to the simple colloid form and will therefore be considered by itself. The cysts have been found to have such close relationship to the adenomata that they may be considered with the latter.

In the study of each type of lesion, a systematic manner of presentation will be pursued as far as possible. First, a tabulated list of the cases, giving the age of the patient at the time of operation, the age of onset, the duration of the disease and the ultimate outcome when possible, will be presented. Following

[1]To these might be added, to make a classification complete, the sarcomata, the fibromata and the mixed tumors, together with acute thyroiditis, all of which are very rare affections and have not occurred in this series.

I wish here to express my thanks to Dr. Pearce for the privilege of using the material at the Bender Laboratory, and also indirectly to Dr. Blumer, whose careful records has made this study possible. Also I wish to thank the surgeons of the Albany Hospital, especially Drs. Vander Veer, Macdonald and Elting, who have allowed me access to their clinical records.

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this one or more typical cases will be related in detail, with a brief clinical note and a complete pathologic study. When other cases offer points of interest or importance, not already covered in the quoted cases, attention will be directed to these special features in the general discussion. The etiologic and pathologic significance of the group as a whole will then be considered, and finally, after the consideration of each separate group, a résumé will be made of the main points in diagnosis and treatment of thyroid lesions in general.

I—SIMPLE HYPERTROPHY (COLLOID HYPERTROPHY). TWENTY-SIX CASES.

No.	Age of onset.	Age at operation.	Duration.
1	22	23	16 months.
2	24	25	12 months.
3	.....	68	.....
4	13	13	6 months.
5	.....	.....	.....
6	.....	.....	.....
7	.....	30	.....
8	24	25	12 months.
9	.....	43	.....
10	.....	42	several years.
11	42	43	1½ years.
12	40	43	3 years.
13	16	18	2 years.
14	24	27	3½ years.
15	13	23	10 years.
16	13	15	2 years.
17	32	40	8½ years.
18	44	62	18 years.
19	11	18	7 years.
20	.....	.....	.....
21	15	49	34 years.
22	.....	47	.....
23	36	53	17 years.
24	.....	.....	.....
25	.....	56	.....
26	.....	28	.....

Average at onset, 24 years; average age at operation, 36 years; average duration, 7 years, 4 months; females, 21; males, 3; sex not stated, 2.

Case I.—(Path. No. 05-1011.) Male, aged 18; for 7 years has had enlargement of the neck with at times dyspnœa and some prominence of the eyes noticed. His mother is said to have had the same condition.

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Physical Examination.—A symmetrical enlargement of the entire neck anteriorly and laterally, but slightly greater on the right side, is seen. The enlargement extends outward and backward on either side and is felt deep under the sterno-cleidomastoid muscle.

Operation, June 15, 1905, by Dr. G. E. Beilby. Cocaine. Transverse Kocher incision. The thyroid gland, with the exception of a portion of the upper part of the left lobe about 4x4 cm. in extent, was removed without difficulty. The right lobe is larger than the left and extends more deeply into the tissues.

Patient made an excellent recovery. In January, 1906, the patient's health was excellent.

Pathology.—Macroscopic Examination: Specimen consists of a thyroid gland showing distinctly right, left and median lobes. Weight, 530 grammes. Left and median lobes have been removed entire; a portion of right lobe is absent. The left lobe measures 12.5x5x4 cm., the median 4x2 cm. and the right 10x5x6 cm. The mass is definitely encapsulated, of firm consistence, distinctly lobulated and of a dark red color. The blood-vessels of the capsule are very large and tortuous. The right and left lobes are somewhat symmetrical and more or less kidney-shaped, with flattening of the posterior surfaces. The right lobe is of somewhat greater diameter anterio-posteriorly than the left. On section right lobe is seen to be grayish yellow in color and from the cut surface escapes a thick gelatinous material. It is lobulated; the lobules being composed of numerous alveolar spaces the walls of which are formed of rather firm bands of connective tissue and in which is a colloid material of a clear translucent appearance. Very many large blood-vessels are seen on section. No cysts are present. The left lobe is similar in all respects to the right.

Microscopic Examination.—Sections from four different portions of mass all show practically the same condition. In general the structure is that of the normal thyroid gland. The gland acini, however, are greatly dilated and filled with a homogeneous colloid material which stains with eosin. These acini for the most part are lined with a single layer of cuboidal epithelium. In many are blood-corpuscles and cholesterin crystals. The capsule of the gland is very delicate, and there is but a moderate amount of connective tissue throughout the gland substance.

Microscopic Diagnosis.—Simple colloid hypertrophy.

CASE II.—(Path. No. 97-5). Female, aged 23, single. History of enlargement of the neck in the region of the thyroid for 13 years. The enlargement has gradually increased. Recently patient has complained of dyspnœa, dysphagia and nervousness. No exophthalmus.

Operation.—November 15, 1897, by Dr. Macdonald.

Pathology.—Macroscopic Examination: Specimen consists of a lobulated mass of tissue of firm consistence, measuring 12x6x4 cm. It is divisible into two lateral lobes and a central portion, which probably represents the original thyroid gland. The surface is smooth for the most part, but in places, particularly posteriorly, is covered by vascular adhesions. The cut surface has a yellowish gray color, is irregularly divided into lobules, and is dotted here and there with cysts, containing a yellow,

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jelly-like material. This surface is smooth and glistening and covered with a translucent, sticky material. There are no signs of old or recent hæmorrhage into the gland substance.

Microscopic Examination.—The tumor consists of tissue having in a general way the appearance of thyroid gland. It differs from this structure only in a marked increase in the size of many of the gland acini which contains a large amount of colloid material. *Microscopic Diagnosis.*—Simply colloid hypertrophy.

CASE III.—(Path. No. 05-996). Male, aged 60. History of goitre for 18 years which, though of large size, caused no symptoms until two months ago, when severe dyspnœa and dysphagia developed.

Operation.—September 26, 1905, by Dr. Elting.

Pathology.—Macroscopic Examinations: Specimen consists of a flattened encapsulated dark red mass of tissue measuring 11x8x5 cm. having the general appearance of an enlarged thyroid gland. One surface is regular in form and is covered by fine adhesions; the other surface shows irregular lobulations separated one from another by deep fissures. The capsule contains a rich plexus of veins. Loosely attached to this mass is another similarly encapsulated mass 6x3.5x2.5 cm. which is pinkish red in color, lobulated and the seat of numerous small cysts. The surface is covered with fine adhesions. The cut surface of the larger mass shows a greatly thickened capsule surrounding well-marked lobules which have a smooth, glary surface, and appear to be filled with colloid material. The smaller mass on section shows a similar capsule, paler in color and with smaller, less well-marked lobules, and numerous small cysts filled with yellow blood-stained fluid.

Microscopic Examination.—Sections show structure of thyroid gland with capsule greatly thickened. The acini are greatly increased in size and number and filled with colloid. There is no increase in the interstitial substance or in the cells lining the acini.

Microscopic Diagnosis.—Simple colloid hypertrophy.

These three cases illustrate very well this type of enlargement. It is characterized clinically by symmetrical increase in size, which is usually not rapid but extends often over many years. It is true that one lobe may be larger than the other, but the essential change is a diffuse involvement, and the term "simple goitre" or "simple hypertrophy" should be applied only to those lesions which thus involve the entire gland.

Histologically, the characteristic feature is a dilatation of the thyroid vesicles, the result of the increased colloid secretion. There is lack of uniformity in the size of the vesicles, but it is rare to observe any portion of the gland which shows normal vesicles. The connective-tissue stroma in the earlier cases is often found to be somewhat scant, but definite lobulations can always be made out. After the condition has existed for a number of years secondary changes may produce a rather complex

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picture. These are most frequently hæmorrhage into the alveoli, with associated degeneration and pigmentation in focal areas. Infiltration of leucocytes and lymphoid and plasma-cells is not infrequent. The connective tissue in cases of long standing is usually very abundant. Calcification is common as a late degenerate change. Cysts of large size in a gland showing simple hypertrophy have not been observed. Minute smooth walled cysts formed evidently by the rupture of the walls of adjacent vesicles, with fusion of their colloid contents, are commonly present.

Etiology.—It will be remembered that in the early embryonic thyroid colloid is not present in the epithelial vesicles. The colloid secretion makes its appearance at about the time of birth and first in small amounts, but with the advancing age of the child the individual vesicles show increased dilatation; the gland probably attaining its most active secretory stage during youth or early adult life. An enlargement of the thyroid at this period is very common, but it usually disappears at twenty-three to thirty years of age. This enlargement probably represents a simple hypertrophy of the organ. In explaining this condition of simple hypertrophy, then, it seems proper to infer that in a certain number of cases, instead of a subsidence of this physiologic hypertrophy, the process in an exaggerated form continues and a permanent hypertrophy is the result. In this series it is seen that while before twenty years of age only four cases came to operation, in six the age of onset was before twenty and in four others, in which the age of onset is stated, it was between twenty and thirty years, making nearly one-half of the recorded cases appearing either in youth or early adult life. Pregnancy in a few instances has apparently been the exciting cause.

In simple hypertrophy there is as a rule no symptoms except those produced by pressure upon the structures of the neck. Circulatory disturbances with extreme enlargement seem to be fairly common. Vertigo, which is frequently a symptom, is due, possibly, to pressure of the enlarged gland upon the blood-vessels of the neck. The duration of the condition varies greatly, for the patient seldom seeks advice until the pressure symptoms become severe. Mere deformity causes no concern, but when respiration or deglutition becomes difficult relief is sought. The periods of time represented in these cases vary from a few months to thirty-four years. The size to which the gland may attain also varies greatly. There seems to be no relation between

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the duration of the condition and the size of the gland. The case showing the most extensive hypertrophy in this series is Case I, quoted above.

In the condition of simple hypertrophy, then, three things may occur. First, there may be a subsidence of the active secretory process after puberty or during young adult life, and a diminution of the amount of colloid present with a return of the gland to its normal size. These are the cases of moderate enlargement. Second, the epithelium may cease to secrete colloid material after a certain age is reached, but fail to undergo retrogressive changes and the enlargement become a permanent one. Instances of this nature are frequent. The hypertrophy is of moderate degree causing as a rule no subjective symptoms, and but rarely demanding operation. Third, a condition similar to No. 2, in which in addition we see in later life, after a quiescence of many years, a rapid increase in the size of the already hypertrophied organ. This enlargement is apparently due to two causes —an increase in the colloid secretion, as observed in the primary enlargement, and an actual reproduction (hyperplasia) of thyroid tissue. This latter is apparently the process present in the majority of cases. Only a portion of the gland may be secondarily affected. The following case, which clinically was considered to be malignant, illustrates this type.[1]

Case IV.—(Path. No. 05-1114). Female, aged 53, goitre with slow growth for 17 years. First began during pregnancy. During the past seven months the enlargement has been rapid and confined chiefly to the left lobe. Dyspnœa and dysphagia marked.

Operation, October 25, 1905, by Dr. Vander Veer. Considerable difficulty was experienced in removing the gland, owing to its deep attachments.

Pathology.—Macroscopic Examination: Usual appearance of old hypertrophic gland with increase of connective tissue, degeneration and calcification in areas, but in addition a large amount of comparatively normal thyroid tissue, differing perhaps in that it has a more cellular appearance.

Microscopic Examination.—The sections show in general a simple hypertrophy with fairly large colloid vesicles lined by the usual epithelium. Here and there, however, are areas of small vesicles, some filled with cells and others containing a little colloid representing young thyroid tissue in various degrees of development. Small masses of epithelial cells are not infrequently observed outside of the colloid vesicle and probably represent focal zones of new thyroid tissue or compressed epithelial vesicles.

[1] Under "Carcinoma" will be discussed the frequency with which hypertrophied glands of this nature undergo carcinomatous changes.

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The histologic appearance in this case suggested the possibility of carcinoma. There is, however, no definite evidence of invasion of the old connective-tissue stroma by the new-formed thyroid tissue. This is a histologic picture frequently observed in cases of old simple hypertrophy in which there has occurred recent growth. Patient made a good recovery from the operation and was well six weeks later.

II.—ADENOMA; 9 CASES

No.	Age of Onset.	Age at operation.	Duration.
1		38	
2	16	21	5 years.
3	37	55	18 years.
4		24	
5	18	23	5 years.
6	25	26	1 year.
7	35	40	5 years.
8	28	30	2 years.
9		43	

Average age at onset, 26 years; average age at operation, 33 years; average duration, 7 years; female, 8; male, 1.

CASE V.—(Path. No. 755). Male, aged 55. Onset of tumor 18 years ago in region of thyroid. Has grown larger during the last two years. No symptoms except tumor.

Operation, September 26, 1904, by Dr. Elting. Excision of tumor of left lobe. The right lobe and isthmus seemed normal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor of the thyroid, measuring 8x6x3 cm. Tumor mass has been cut open. On section it presents a rough nodular surface mottled with dark red areas. Surrounding these is a brownish yellow zone and still further out a deep red finely granular zone. The lighter areas are approximately 1x.5 cm., the dark red areas measuring about 2x1 cm.

Miscroscopic Examination.—There is distinct hyperplasia of both glandular and interstitial tissue, the glandular elements in places being massed together and compressed, with irregular outlines; in other places dilated and filled with colloid material; in still other areas the glandular elements are atrophied with marked increase of interstitial tissue, which is highly œdematous and hyaline.

Microscopic Diagnosis.—Mixed adenoma of the thyroid gland.

CASE VI.—(Path. No. 05-1207). Female, aged 23. Tumor for 5 years. Rapid enlargement during the past eight months; dyspnœa. Tumor of the right lobe pushing the trachea and larnyx to the left.

Operation, November 14, 1905, by Dr. Elting.

Pathology.—Macroscopic Examination: Specimen consists of a definitely encapsulated tumor 10x5x8x6 cm. Capsule is smooth and apparently free

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from adhesions. At one pole is a small irregular tumor. The capsule is very dense and fibrous. On section the tumor presents a uniform grayish appearance. Tissue is exceedingly soft and friable. No fibrous bands are seen. In the centre of the mass the tissue is disintegrated and there is found a small cavity filled with blood-stained colloid material. On section, the smaller tumor attached to one pole of the larger has the appearance of normal thyroid tissue and evidently represents the isthmus of the thyroid gland.

Microscopic Examination.—(See Fig. 1.) The general structure of thyroid tissue can be seen, but there are no definite lobulations as are found in the normal and hypertrophied gland. The thyroid vesicles, however, are greatly enlarged and filled with a homogeneous colloid material which stains with eosin. In some areas epithelium lining the individual vesicles has disappeared and their contained colloid has coalesced, forming large irregular pink staining masses. Throughout the colloid material is seen isolated cells and clumps of cells which stain poorly and which represent the desquamated epithelium. There are also numerous red-blood cells. When an epithelial lining is present instead of a single layer of cells we see often several layers, and here the cells stain very poorly and have no definite arrangement. The connective-tissue stroma is very scant and the alveolar walls are delicate. There are a few small epithelial vesicles which contain no colloid and represent young thyroid tissue. The general picture is one of early degeneration.

Microscopic Diagnosis.—Colloid adenoma of the thyroid.

CASE VII.—(Path. No. 64-5.) Female, aged 26. Duration of illness 8 months. The prominent symptoms are pain, dyspnœa and dysphagia.

Operation, February 20, 1899, by Dr. Vander Veer. No note on operation.

Pathology.—Macroscopic Examination: Specimen consists of a globular nodule measuring 4x3x1.5 cm. It is completely encapsulated. Its outer surface is covered here and there with torn adhesions which are attached to the capsule. The nodule is soft in consistence. On section the cut surface bulges somewhat; it is mostly of a gray-white color and rather translucent in appearance. Scattered through it are a few whiter areas suggestive of necrosis and one or two minute hæmorrhagic points.

Microscopic Examination.—The section shows both the capsule and tumor substance. The capsule is composed of several layers of fibrous tissue, in the outermost layer of which can be seen compressed thyroid vesicles probably the result of the encroachment of the growth upon the normal gland-tissue. The tumor proper is made up of closely packed epithelial vesicles, which as a rule are empty or have only a cellular content. In this respect the tissue resembles that of the fœtal thyroid, but differs in that the cells are of a higher type. In some of the vesicles, farthest from the periphery, there is a small amount of colloid present, this probably representing the oldest portion of the growth. The connective-tissue stroma is very scant and there are no lobulations visible.

Microscopic Diagnosis.—Mixed adenoma of the thyroid gland.

CASE VIII.—(Path. No. 05-95.) Female, aged 21 years, married. A tumor the size of a marble appeared in the region of the right lobe of

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Plate IV.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

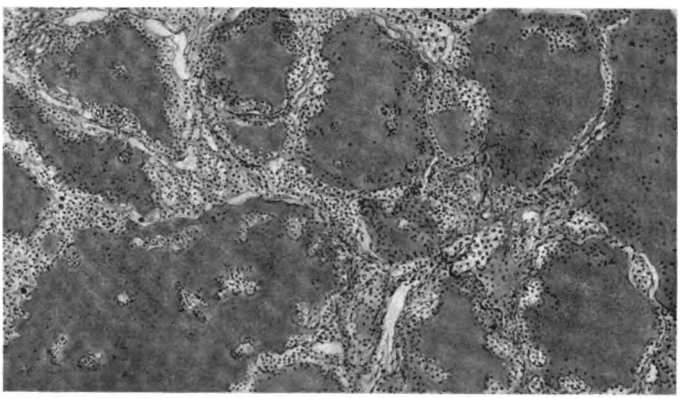

Fig. 1.—Microscopic drawing of a colloid adenoma.
The illustration shows that the thyroid vesicles are distended with a homogeneous colloid substance in which are clumps of epithelium and isolated epithelial cells.

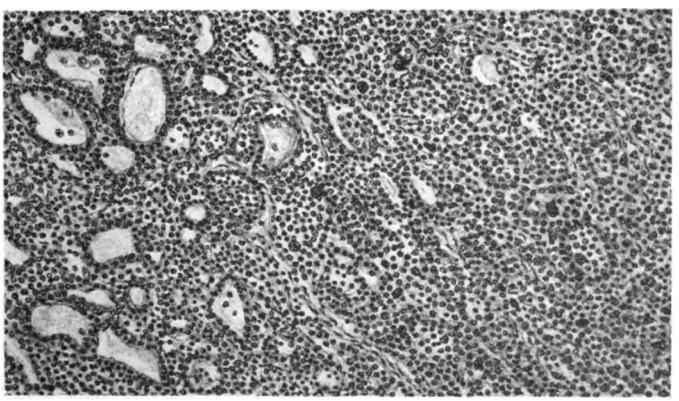

Fig. 2.—Microscopic drawing of a recurrent adenoma 4 oc., 3 obj., Leitz.
The left portion of the drawing shows tissue containing a few apparently normal thyroid vesicles. The right portion shows tissue in which no normal vesicles are present, but composed of epithelial cells, having no typical arrangement, and in a few of which a large, irregular, and deep staining nucleus is seen.

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the thyroid five years ago, two years after her last child was born, and has gradually increased in size since. Dyspnœa has been more marked of late.

Operation, January, 1905, by Dr. Elting. Ether. "The patient took the anæsthetic very badly. Resuscitation was necessary during the operation. The tumor was removed through an incision along the anterior border of the right sterno-cleidomastoid muscle."

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor measuring 2.5x2x1.5 cm., enclosed in a yellowish white capsule. On section it is fairly firm in consistence and presents a brownish white surface. Very little connective-tissue stroma can be seen.

Microscopic Examination.—Section shows a thick fibrous capsule with normal appearing thyroid tissue in its outer layer. The structure of thyroid gland can be made out, but the individual vesicles are small as a rule and contain no colloid. In a few areas the vesicles are elongated and assume a tortuous tubular shape. The connective tissue shows hyaline degeneration and œdema.

Microscopic Diagnosis.—Pure adenoma of the thyroid.

Etiology.—These adenomata comprise the solid non-malignant encapsulated tumors of the thyroid. They may arise within the tissue of the thyroid gland, without being connected with its capsule, or at some distance from the gland. They occur usually singly, but in two instances in my series they occurred as multiple tumors of one lobe. In one of these were present two smaller tumors, each about 3 cm. in diameter, attached to either pole of a larger tumor 8x3x3 cm. in size. In the other a tumor of the left lobe 8x6x3 cm. in size had attached to its capsule at one pole a small nodule about 2 cm. in diameter, which macroscopically had the same appearance as the larger tumor.

As to the location, five occurred within or apparently arose from the right lobe, two from the isthmus, and one from the left lobe, and in one instance the situation was not stated. These tumors are in my experience usually of small size. The largest was 10x8x6 cm. and the smallest 3 cm. The average diameter was about 5 or 6 cm.

Clinically the adenomata are not as a rule difficult to recognize. They are hard and firm, freely movable, and generally present no symptoms except tumor. By their pressure upon the trachea or œsophagus they may produce dyspnœa or dysphagia and in two instances the extreme nervousness of the patient was ascribed to such pressure. The age of onset seems to correspond to that of adenomata in other glands of the body, occur-

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ring during youth or early adult life, when glandular activities are at their height. The age of onset was generally between 16 and 35 years; five or over one-half between the twentieth and thirtieth years. From the fact that these tumors produce no subjective symptoms, and that their growth is as a rule slow, it is often many years before the patient seeks surgical relief. It is probable that these tumors are far more common than indicated by this series, for it is only when they produce pressure symptoms or cause considerable disfigurement that the advice of the surgeon is sought.

No important etiologic factors, other than the age, can be determined. In one case, the tumor appeared two weeks after confinement.

There is nothing in the records to indicate that the thyroid gland in these cases was abnormal. Where observations were made by the operator, it is noted that the gland appeared normal.

Pathology.—The adenomata are definitely encapsulated tumors, usually smooth, but occasionally somewhat nodular or lobulated. The tumors vary considerably in consistence but are usually soft.

Two distinct varieties may be recognized, depending upon the type of vesicle. In the first, which we may designate as *pure adenoma,* the growth is found to be composed of closely-packed epithelial vesicles, containing little or no colloid and very small amount of connective tissue. Many of the acini are seen to be filled with epithelial cells. In the other variety, we have a condition in which histologically the picture very closely simulates that of simple hypertrophy. These we may designate as *colloid adenomata.* The epithelial vesicles are dilated and filled with colloid material. There is usually but a single lining layer of epithelium.

An interesting feature of these tumors is their tendency to undergo various degenerative changes. The colloid adenoma resembles somewhat histologically the simple hypertrophy, but differs, however, in some important respects. Thus the stroma is less abundant, the walls of the vesicles are thinner, and the epithelial cells lining the vesicles in the hypertrophied organ are of a lower type than those in the colloid adenoma. To make a distinction between simple hypertrophy and adenoma is easy clinically and from a macroscopic examination of the specimen, but upon histologic examination distinct differences in structure are not so evident.

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Briefly stated, the main differences seem to be these:

(*a*) As to the epithelium lining the vesicles. In the adenoma we find the cell tending to a columnar character, while in the hypertrophy the cells appear more compressed and assume the appearance of a cuboidal type.

(*b*) As to the contents. Colloid. In the early adenoma, epithelial tissue is the one tissue present. Small amounts of colloid are visible, but this is not seen in appreciable amounts until a later stage. In this later stage the colloid is increased markedly in amount, and approaches as to quantity the amount which is visible in the hypertrophied gland. Besides this colloid material, which in certain amounts is normally present, the alveoli may also contain desquamated epithelium and red-blood cells. In the colloid adenoma there is usually present a large number of epithelial cells within the alveolus, which stands in marked contrast to the hypertrophy where no desquamation is evident. Again in the adenoma small hæmorrhages into the alveoli are more common.

(*c*) As to the stroma. In the adenoma scarcely any connective tissue stroma is visible, the vesicles with or without colloid material being closely packed together. In the hypertrophy, however, while a number of vesicles containing considerable colloid are in close proximity, being separated by small amounts of connective tissue, the groups of vesicles are isolated and between these groups dense and rather large amounts of connective tissue are visible.

Depending upon the secretory activity of the epithelial cells of the adenomata, a complex picture may be produced.

First, All of the epithelial cells may begin to secrete actively and varying amounts of colloid may appear within the alveolus, producing the *colloid adenoma.*

Second, All the epithelial cells may fail to secrete, and then we have a type of gland in which no colloid material is visible, resembling in many respects the type of tumor described as *fœtal* adenoma but differing in that the vesicle is not solid—*i. e.,* made up of several layers of epithelial cells, but is merely an alveolus lined by a single layer of cells in which no colloid material is evident.

Third, A number of the cells may remain dormant while the remainder are secreting colloid material, thus presenting the picture which many authors describe as *mixed adenoma.*

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Cyst Formations.—Here I wish to emphasize the fact that undoubtedly a large percentage of cysts of the thyroid have their origin in adenomata. Very frequently we find in the walls of cysts thyroid tissue resembling simple hypertrophy. Cyst formations however in thyroids that have undergone simple hypertrophy is an extremely rare occurrence. None of the cases reported in this series show aught but minute cysts formed by the rupture of the walls of a few adjacent vesicles and the coalescence of their contained colloid. The adenomata, however, appear very prone to undergo degeneration with the formation of cysts. In Case VI it was seen that the tumor presented distinct evidences at its center of beginning cystic formation.

III.—Recurrent Adenoma. Three Cases—Male 2, Female 1.

The adenomata, as has been shown in the preceding section, occur singly as a rule and do not present histologically or clinically signs of malignancy. We have, however, three cases in which there has been either recurrence at the site of operation or a subsequent appearance of a similar tumor in other portions of the gland. These were clinically considered to be malignant, and the microscopic study revealed a more or less atypical growth of epithelium.

Case IX.—(Path. Nos. 97-3 and 64-19.) Male, aged 49. Thyroid tumor appeared twenty years ago and gradually increased in size up to five years ago, causing dyspnœa and dysphagia.

Operation, February 6, 1897, by Dr. Macdonald. Removal of tumor. Five months later a similar tumor appeared in the isthmus and gradually increased in size for four and a half years; and now presents as a firm apparently encapsulated tumor in median line of neck about 4x6 cm. in size. The lateral lobes of the thyroid show slight enlargement. The surgeon, Dr. Macdonald, considered the growth to be malignant and the entire gland was therefore removed.

Pathology.—(First operation.) Macroscopic Examination: Specimen consists of a portion of the thyroid gland measuring 9x6 cm. The outer surface presents a mottled appearance, the prevailing color being red, with here and there small areas of discoloration due to hæmorrhage. The surface vessels are distended. On section the specimen shows a large empty cyst, the walls of which are thin and covered by gelatinous substance, probably colloid material. Other cysts are seen of smaller size than the one just described. They are filled with a colloid material and in some are small pea-sized hæmorrhages. Portions of the growth have undergone calcareous degeneration.

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Microscopic Examination.—No definite capsule is seen. The tumor proper is made up of tissue of the same general type as that of the normal thyroid but which shows greater irregularity in the gland acini. The connective-tissue network is moderately augmented; this is evident in the size of the strands. Irregularly distributed throughout the specimen are collections of epithelial cells of the same appearance as those constituting the normal gland structure. The gland spaces are for the most part smaller than normal, though here and there dilated spaces may be seen. All alveoli contain homogeneous pink-staining material, presumably colloid; in a few hæmorrhage has occurred. There is marked hyperplasia of the epithelial cells.

Microscopic Diagnosis.—Adenomatous cysts of the thyroid.

Second Operation.—(Path. No. 64-19.) Macroscopic Examination: Specimen consists of six pieces of tissue which are evidently from the thyroid gland. The largest portion measures 7x8x4 cm. Its outer surface presents a somewhat lobulated appearance and is covered with a smooth membrane to which are attached a few fibrous adhesions. Beneath the membrane the color of the tissue is a light red. On section the tissue is of fairly firm consistence, but varies somewhat in character in the different portions. In some places it presents a semi-translucent grayish white appearance, in others it is darker in color and somewhat more opaque. Considerable portions of the specimen are made up of the colloid material. Here and there are definite calcareous deposits. In one of the smaller portions which measures 7x4x2 cm. the tissue resembles that already described except that an area about 3.5 cm. in diameter is definitely hæmorrhagic. The remaining pieces which compose the specimen are similar in structure to the portions described.

Microscopic Examinations.—We have here the same general type of tissue seen in the tumor removed five years previously. Some of the gland acini are greatly enlarged and filled with colloid material; others are small and have only a cellular content. The epithelium approaches the columnar type and in many places shows no typical arrangement.

Microscopic Diagnosis.—Adenoma of thyroid.

In this case the specimen first removed (97-3) is a cyst which has apparently arisen by degeneration of an adenoma, while the second growth (64-19) presenting the same characteristics clinically, was an adenoma. The significance of this in relation to cysts will be discussed under that heading.

Case X.—(Path. No. 64-26.) Female, aged 45. Tumor of right lobe which first appeared seventeen years ago (1888). After five years it reached the size of a lemon and was removed September, 1893, no pathologic study was made. Four years after first operation (1897) a similar tumor appeared in the left lobe and was recovered six years later (Sep. 21, 1903), by Dr. Macdonald. This tumor the patient states seemed exactly similar to the first one. Both finally produced pressure symptoms upon the trachea and œsophagus, and for relief of these symptoms patient sought operation. With the second tumor there was con-

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siderable pain, and dyspnœa and dysphagia were more pronounced. The description of this tumor follows:

Pathology.—Macroscopic Examination: Specimen consists of a portion of thyroid gland measuring approximately 11x4.5x3.5 cm. Beneath the capsule except in a small portion of the end of the tumor can be seen numerous pea to cherry-sized cysts. In the center of the specimen can be felt a hard stone-like mass the size of a cherry. On section all but a small area at one end of the specimen is seen to be filled with various sized cysts containing a clear colloid material. The wall of one of the larger cysts is completely calcified and measures 2 mm. in thickness.

Microscopic Examination.—The gland alveoli are numerous and for the most part distended by homogeneous colloid material. Some contain also desquamated cells and leucocytes many of which are loaded with pigment. The alveoli surrounding the more distended alveoli are small and arranged concentrically. Other areas show small irregularly developed alveoli. Several are irregular and without any distinct limiting wall and contain a bluish pink mucoid-like material, blood pigment and elongated connective-tissue nuclei. The interalveolar tissue shows hyaline degeneration in places.

Microscopic Diagnosis.—Adenoma with hæmorrhage and calcification and a tendency to an atypical growth of the epithelium.

About two months ago, two years after the second operation, a tumor appeared in median line of the neck and has slowly increased in size. This tumor is clinically an adenoma. There is no evidence of recurrence at the sites of previous operations. Patient's general health is excellent. The patient is considering an operation.

Case XI.—(Path. No. 97-2.) Male, aged 60. Tumor removed from the region of the right lobe of the thyroid by Dr. Macdonald nine years ago.

Pathology.—Macroscopic Examination: Specimen consists of a mass almost the exact size and shape of a kidney. The surface is irregular and in places it is covered by a distinct capsule which is somewhat hæmorrhagic. In other places patches of connective tissue containing large blood-vessels lie on the surface. It is somewhat lobulated and of a brownish yellow color. On section at one point is seen a cyst-like cavity containing a friable grumous material of a yellowish color, slightly viscid and apparently cell-detritus. The remainder of the tumor can be divided into a cortical and medullary portion. The cortical portion averages about 1.5 cm. in width and is distinguished from the medullary by its light color and more or less radial striation due to the presence in its substance of fine bands of connective tissue. The medullary substance is distinctly pinker in color than the cortical, and the bands of connective tissue which traverse it have no distinct or regular distribution. The consistence of the tumor as a whole is firm, the cortical substance perhaps being a little firmer. Distinct areas of calcification are present.

Microscopic Examination.—(See Fig. II.) Sections show the tumor to consist of a capsule and tumor substance. The capsule is for the most part made up of fibrous tissue. Here and there, however, it contains small collections of cells of the same type as the gland-cells, and

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it is evidently formed of compressed gland substance. The tumor itself is composed of a tissue of the same general type as normal thyroid tissue. It differs in the greater irregularity and shape of the gland acini. Near the capsule the connective-tissue network often runs in parallel striæ passing from the capsule into the depths. In the deeper parts of the tumor this cannot be made out. The colloid material in one or two places has undergone calcification.

Microscopic Diagnosis.—Adenoma of the thyroid.

Recurrence in same location after seven years. This second growth was an encapsulated tumor which had reached the size of a hen's egg. Specimen not saved for pathologic study.

A year after the removal of the second growth (April, 1903) there was again a recurrence which soon reached considerable size. On consulting a surgeon at this time the process was considered malignant and operation not advised. From this time until January, 1906, about one and one-half years, when patient was last seen, there has been constant increase in the size of the primary growth, which now measures 7x6 cm. in size. It is located in the right lobe of the thyroid and extends apparently deep into the neck. Near the upper pole of this tumor there is a second mass, which made its appearance about one year ago. This is entirely distinct from the older tumor, is superficial, and has no deep attachments. It is ovoid in shape, 5x4 cm. in size, and moves about freely underneath skin, which is nowhere adherent over either tumor. Patient has thus far refused operation.

We have then in this case a thyroid tumor which has returned twice after removal, the condition extending in all over a period of nine years, and in which there has developed now in the region of the recurrent tumor a secondary growth. The patient is still in fair general health but suffers from the effects of pressure. The question of carcinoma arises. The long duration would almost exclude this possibility. The growth, while of large size, is as far as can be determined, encapsulated, and affects the health of the patient only by its mechanical presence. Histologically, the first growth removed can be characterized only as an adenoma, though it does present an unusual picture, similar to that in the other two cases described in this group. An interesting feature is that in all of these cases the patients are now over 40 years of age. In one the onset of the first growth was at 51 and in the other two, one at 29 and the other at 32 years of age, thus differing from the usual history of adenoma.

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IV.—Cysts. 12 Cases.

No.	Age of onset.	Age at operation.	Duration.
1	10	16	6 years.
2	21	26	5 years.
3		27	
4	17	26	9 years.
5	38	42	4 years.
6	33	41	8 years.
7	36	43	7 years.
8	15	24	9 years.
9	25	33	8 years.
10	19	20	18 months.
11	49	49	4 months.
12	39	43	4 years.

Average age of onset, 27 years and 6 months; average age at operation, 32 years and 6 months; average duration of disease, 6 years; females 7, males 3; sex not stated 2.

We recognize three main types of thyroid cysts, *simple, hæmorrhagic,* and *adenomatous cysts.*[1]

Simple Cysts.—Three cases.

Case XII.—(Path. No. 06-197.) Male, aged 16 years. When six years of age his parents noticed a small lump about the size of a hickory-nut in the region of the left lobe of the thyroid. This increased very little in size until four years ago, since which time there has been slow but gradual enlargement. There is no exophthalmus or tremor, but the boy is of a nervous disposition.

Operation, January 22, 1905, by Dr. Beilby. Anæsthetic, cocaine. In the region of the left lobe of the thyroid is found a smooth ovoid tumor about 5x9 cm. with its larger diameter extending from the thyroid cartilage towards the ear. No lobulations can be made out. The tumor is very tense and no definite fluctuation can be determined. It is attached to the larynx and moves up and down perceptibly on swallowing. The cyst was excised without rupture. The thyroid tissue about the cyst appears normal.

Pathology.—Macroscopic Examination: Specimen consists of a cyst of the thyroid gland measuring about 6x9 cm. in size. Its outer surface is smooth and only at the pole can thyroid tissue be seen. On opening the cyst the walls are found to be very thick and fibrous. The contents of the cyst is a brownish translucent fluid with numerous oil-globules floating about in it. The inner surface of the cyst-wall is very white

[1] In addition to these, occur the small multiple cysts found with great frequency in the simple hypertrophic gland. They never attain any great size and are undoubtedly caused by the coalescence of two or more distended vesicles with fusion of their colloid contents. Clinically, they never produce any symptoms and are only of pathologic interest.

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and fibrous and is covered with many flakes of fibrin and some atheromatous patches. One small area of the thyroid tissue 1x1.5 cm. projects from the inner wall of the cyst.

Microscopic Examination.—Cyst-wall: outer layer of loose fibrous connective tissue with blood-vessels and a very cellular central zone. At first glance these cells look like lymphoid cells, but the presence here and there of small amounts of colloid material leads to the conclusion that they represent greatly compressed thyroid vesicles with atrophied epithelium. The next layer is the inner wall of the cyst, which is composed of loose lamellæ of tissue and masses of blood-corpuscles, suggesting an organized blood clot.

Microscopic Diagnosis.—Simple cyst of thyroid.

At present, one year after operation, patient is perfectly well.

This is the type of a thin-walled cyst. They occur in glands that are apparently normal. The cyst-wall is composed of compressed thyroid tissue. The inner wall is usually smooth and fibrous but may be lined with a mass of epithelial cells. The contents is usually fluid but varies both in color and consistence, the color depending on the amount of blood and the consistence on the admixture of colloid.

Hæmorrhagic Cysts. One case.

The following case illustrating this type, is perhaps almost unique.

CASE XIII.—(Path. No. 195.) Male, aged 41. Eight years ago patient fell backward down stairs. Noticed at once, following the fall, a swelling in the region of the right lobe of the thyroid gland. This increased in size but little until a few days previous to operation, when a rapid enlargement occurred. This was accompanied by a constant dull pain for which the patient sought advice.

Operation, March 16, 1904, by Dr. Elting. Nitrous oxide and ether. Excision of the right lobe of the thyroid. 50 c.c. of brownish fluid was evacuated from the cyst during its removal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated mass, evidently comprising the entire right lobe of the thyroid gland. It measures 10x5x4 cm. On section a large cavity is found from which was evacuated 50 c.c. of reddish brown fluid containing necrotic tissue. The necrotic material is both free in the cavity and adherent to the walls of the cyst. Here and there in the walls are found calcified areas, none larger than 5 mm. in diameter. The wall of the cyst averages about 5 or 6 mm. in thickness.

Microscopic Examination.—Sections show the cyst-wall to be composed of thyroid tissue, in general fibrous, but in some areas quite normal. There are areas of hemorrhage and necrosis. In these areas and surrounding them is an extensive infiltration with polynuclear leucocytes, though in general the tissue is infiltrated with lymphoid—and plasma-cells. The picture everywhere presented is that of chronic inflammation with tissue degeneration and focal areas of necrosis. The type of thyroid vesicle where it can be made out is that of the normal gland.

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Microscopic Diagnosis.—Hæmorrhagic cyst with chronic thyroiditis, hæmorrhage and necrosis.

Hæmorrhage has always been assigned as an important factor in the production of thyroid cysts. The presence of hæmorrhage, recent or old, in cyst contents or its walls is an almost constant observation. It seems probable, however, that this is much more commonly a secondary process than the true etiologic factor. That a primary hæmorrhage, produced either by violent trauma, or the rupture of a small blood-vessel from any cause within the substance of the thyroid gland, is capable of producing later a cyst there can be no doubt.

Adenomatous Cysts.—Ten cases.

That the adenomata play such an important rôle in the production of cysts seems not to have been generally recognized. In this series, 70 per cent., or 10 of the 14 cases, present evidence of having arisen from this type of tumor.

CASE XIV.—(Path. No. 05-010.) Female, aged 26. Tumor of neck nine years, gradual increase in size, more rapid during the last year. Dyspnœa and tachycardia on exertion. Pulse constantly 104-106. Marked harshness of voice. Complains of headache and pain in right ear. Tumor is situated in median line and moves with deglutition.

Operation, July 17, 1905, by Dr. Beilby. Cocaine. Transverse incision. Excision of cyst of isthmus. The remainder of the thyroid gland appeared normal.

Pathology.—Macroscopic Examination: Specimen consists of a thick walled cyst of the thyroid which was removed at operation without rupture. It is nearly globular in shape but slightly flattened in its anterior-posterior diameter. It measures 7.5x5.5 cm. Its capsule is of a pink color, very delicate and easily torn. The blood-vessels are large and tortuous. It is rather soft and fluctuant. On section it is found to contain a brownish bloody fluid. This cavity is approximately 4.5x3 cm. in size. The wall of this cyst measures from 5 to 15 mm. in thickness and seems for the most part to be composed of apparently normal thyroid tissue. There are some areas, however, which resemble glandular hyperplasia. Again other areas show hæmorrhage and necrosis. Blood-vessels are large and numerous.

Microscopic Examination.—Section through cyst-wall shows a thick capsule, which has apparently been formed by compression of thyroid tissue. Scattered throughout are many normal thyroid cells and in some areas are acini filled with colloid material and lined with cuboidal epithelium. From this capsule strands of connective tissue extend to the deeper portion of the cyst wall and form a definite connective-tissue framework, presenting somewhat the histologic structure of thyroid acini. These spaces, however, are packed with what are apparently desquamated epithelial cells. A few normal acini are noticed, which

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are filled with colloid material. Other sections show in addition free masses of red-blood corpuscles, and marked hyaline degeneration of the connective tissue.

Microscopic Diagnosis.—Cyst in a *mixed adenoma.*

At present, eight months after operation, the patient is in excellent health. The huskiness of her voice has largely disappeared, her pulse has dropped ten to twelve beats per minute, and she is not so nervous as before operation.

CASE XV.—(Path. No. 64-23.) Female, aged 26. Has had a tumor in the right side of the neck in the region of the thyroid for five years. Tumor first appeared during first pregnancy. There has been a gradual slow increase in size up to three years ago, when after the birth of her second child the growth became more rapid.

Pathology.—Macroscopic Examination: Specimen consists of a globular cystic mass 5x3.3x2.5 cm., the outer surface of which is smooth and encapsulated. On section the cyst contents are found to consist of a brownish fluid. The cyst wall is smooth. The cyst originates in the thyroid gland, and to its outer surface fragments of normal thyroid-tissue are adherent.

Microscopic Examination.—The capsule is composed apparently of compressed thyroid alveoli. Within the capsule proper the tissue has the structure of thyroid and very slightly approaches the characteristic fœtal type of gland. No colloid is visible.

Microscopic Diagnosis.—Cyst in a pure adenoma.

CASE XVI.—(Path. No. 97-4.) Female, aged 20; has had a tumor in the region of the isthmus of the thyroid for eighteen months.

Operation, October 19, 1897, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an oval piece of tissue 4.5x3.5x2.5 cm. It is for the most part cystic, the cystic contents having been removed, leaving a cavity which occupies about two-thirds of the tumor, the upper third consisting of a solid mass of tissue. The outer surface of the tumor is moderately smooth, but here and there are the remains of adhesions. The cyst-cavity is the size of a walnut and its walls are thin, averaging about 1 mm. in thickness. The inner surface is very irregular, and is traversed here and there by raised bands. The color varies from pinkish to grayish white. Secondary cysts varying from those the size of a pin-head to those the size of a pea can be made out in the walls. They contain a mucilaginous yellowish-brown fluid. In places on the inner surface of the cavity are areas of calcareous deposit. The solid portion of the tumor is only moderately firm in consistency and measures 2x1 cm. Its cut surface is of a yellowish gelatinous appearance. It contains a number of small cysts filled with fluid, which varies in color from a light to a dark brown.

Microscopic Examination.—The tumor on section presents varying appearances. In some places it has the ordinary appearance of thyroid gland structures, being made up of cavities of various sizes, containing colloid material, between which are cellular bands of tissue. This appearance is confined particularly to the portion of the tumor furthest removed from the cyst cavity. The walls of the cyst cavity are made up

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for the most part, of a firm solid tissue, composed of a basement substance containing numerous epithelial and spindle shaped cells. In this substance are to be seen the compressed remains of the thyroid alveoli and also a very large number of cells containing a yellowish brown pigment, evidently changed blood-pigment. At one point are present in the tumor a number of wedge-shaped spaces, the walls of which are formed by the tumor-tissue. In these are occasional spaces representing a deposit of crystals, presumably cholesterin. The cells about these spaces are multinucleated, apparently foreign-body giant-cells.

Microscopic Diagnosis.—Cyst in a colloid adenoma.

It will be recalled that in discussing the adenomata we recognized two types of thyroid vesicles—one large and containing colloid, and the other smaller in which no colloid was visible; also a third variety, combining the characteristics of these two. In the walls of these cysts we find a histologic structure which exactly corresponds to one or the other of these types. As we might perhaps expect, the colloid adenoma is the variety which most frequently undergoes cystic degeneration. Five, or one-half, of the cysts in this series were of this type. In only one could no colloid be seen in the tissue of the cyst-wall. Four were of the mixed variety. Aside from the histologic evidence of the production of cysts from solid adenomata, we have in certain of the cases a gross appearance indicating beyond doubt that the tumor was originally an adenoma and that degeneration has taken place with a resulting cyst formation. Of importance in this connection is the observation of cholesterin crystals indicating fatty transformation of the epithelial elements. If the process is an early one the cysts may be only of small size and the structure of the adenoma still be retained.

As the degeneration advances and the fluid contents of the cyst is increased in amount, there is compression of the alveoli and later many of the cells may atrophy and the stroma undergo various forms of degeneration, giving widely varying and very complex pictures. The inner layer of the cyst may then be said to be composed of the remains of the adenomatous tissue, while the wall proper represents the fibrous capsule of the original adenoma, and the outer layer, the stroma and compressed alveoli of the surrounding thyroid-tissue. With the enlargement of the cyst and its encroachment upon the surrounding normal thyroid-tissue we often get a lamellated appearance. These lamella are as the result of the successive compressions of the normal gland-tissue, with subsequent atrophy of the epithelial structures, leav-

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ing only the stroma and alveolar walls. Thus fibrous bands of varying thickness appear. Between these layers are often seen normal thyroid vesicles, and vesicles in various stages of atrophy.

The histogenesis of these cysts may be said to be as follows: In the beginning we have an encapsulated adenoma composed of cells which present no colloid secretion. As the growth continues colloid material is secreted and a coalescence of these colloid vesicles in the center of the tumor is to be seen. Hæmorrhage occurs and we have a cystic cavity filled with bloody colloid material. The fibrous capsule of the original adenoma forms the wall of the newly-formed cyst. As the degenerative process continues and the contents of the cyst increases the tumor necessarily becomes larger and pressure is exerted on the surrounding normal tissue, causing atrophy of apparently normal vesicles. As in long continued degenerative processes occurring in other tissues, lime salts may eventually be deposited in the wall of the cyst, giving extensive calcified areas.

V.—Aberrant or Metastatic Thyroid Tumors Which Are Histologically Benign but Clinically Malignant.

One Case.

Case XVII.—(Path. No. 88-68.) Male, aged 65 years. Family and past history not important. Six months ago first noticed a fullness of right side of face and difficulty in breathing through right nostril. Tumor has increased in size rapidly and has been accompanied by considerable pain. At present there is complete occlusion of the right nostril and bulging of right eyeball with inflammation of conjunctiva, and obstruction of tear duct. At the operation by Dr. Vander Veer the antrum of Highmore was opened but only a small portion of the growth was removed. Its extensive character made a complete removal impossible. The clinical diagnosis was sarcoma of antrum.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of tissue removed from the upper jaw. There are one or two pieces of bone, the remainder of the tissue being of a grayish white color and having the appearance of granulation tissue.

Microscopic Examination.—The sections indicate that the tissue is that of the thyroid. Two definite pictures are presented. First, large alveoli filled with colloid, lined usually by a single layer of cubical epithelium, and containing throughout the colloid substance many desquamated epithelial cells which take the stain rather poorly. Second, areas showing epithelial hyperplasia but less tendency to colloid secretion, giving the tissue a more solid cellular appearance. On careful examination of these cellular areas they are found to be composed of closely packed thyroid vesicles, some of fair size but filed with cells which approach a columnar

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type. Hæmorrhages into the alveoli are frequent. Connective tissue stroma is very scant. The tissue shows signs of inflammation in places, containing a number of polynuclear leucocytes.

Microscopic Diagnosis.—Aberrant or metastatic thyroid tumor.

For the further history of the case I am indebted to Dr. Merritt, of Cherry Valley, who writes me that the growth increased very rapidly after the patient left the hospital and finally involved the right eye. The bony structures he thinks were extensively involved as some of the teeth and a portion of the superior maxilla were lost during the course of the disease. To the best of the doctor's recollection and that of the patient's friends, there was no hypertrophy or tumor of the thyroid gland, either previous or subsequent to operation.

To establish a positive diagnosis of *metastatic adenoma of the thyroid,* we must necessarily have at least clinical evidence that a primary adenoma existed in the thyroid gland. This evidence is wanting. If such an adenoma existed it was so small as to escape notice. Whether or not such a primary tumor existed the case is of equal interest.

There are now in the literature records of about 20 cases of tumors apparently metastases from the thyroid, which were histologically benign. As in a number of these instances there has been no apparent primary thyroid lesion, these cases have been considered as *metastases from normal thyroid tissue.* Where a thyroid lesion has been observed it has been that of simple hypertrophy or adenoma, and the metastatic tumor has had a similar histologic structure. These metastases, which may be single or multiple, have occurred most frequently in bone, and have often been removed under the supposition that they were primary growths. Aside from the fact that these tumors are probably of metastatic origin, they present as a rule no other indication of malignancy. Frequently, however, they have been known to recur after removal and a number of cases have thus resulted fatally. Therefore the important question arises, are not these tumors malignant and should they not always be considered as such by the surgeon?

In the case I report the tumor presented clinically every indication of malignancy. Its invasion of tissue was rapid and death was caused in eight months after its onset. As there never was observed any hypertrophy or tumor of the thyroid gland, we can only assume that if this was a metastatic tumor the metastasis was from normal thyroid tissue. As will be noted, however, in the microscopic study, the growth was his-

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tologically a thyroid adenoma and of the type we have described as mixed adenoma.

In the case reported by Oderfeld and Steinhaus[1] the first tumor observed was in the frontal bone. This was removed and histologically found to have the structure of normal thyroid. The patient was again seen after an interval of six months, but no recurrence was evident. After about a year there was a recurrence and also other similar tumors made their appearance, one in the temporal region and one at the sterno-clavicular articulation. Clinically these tumors were considered to be malignant. At the request of the patient the one in the temporal region was removed. This presented a similar structure to the one removed from the forehead one year before. The patient died a few weeks later. Before death a thickening of the under half of the right lobe of the thyroid was noted. A complete autopsy was not permitted, but all visible tumors were removed together with the thyroid gland. Within the substance of the right lobe of the thyroid was found a small nodular thickening 2 cm. in diameter. The remainder of the thyroid appeared normal. The tissues were all carefully sectioned and examined, the authors expecting to find carcinomatous degeneration, but the structure throughout the tumor of the thyroid and the other isolated tumors of the head and neck were uniformly the same, and as they observe had the exact structure of normal thyroid tissue. They regard the small thyroid nodule as the primary tumor and the tumors of the head and neck as metastases.

Etiology.—The fact that we have in these metastatic tumors structures similar or almost identical to the tissue found in the normal gland lends special interest in the etiology of these tumors. In its consideration several factors may be taken into account.

First, Origin from *misplaced embryonal tissue.* The theory which has been advanced by Conheim in which he regards the etiology of malignant growths as due to misplaced embryonic cells might be applied to tumors of this class.

Second, Origin from *aberrant or accessory thyroid.* Murphy in a recent article[2] calls special attention to a group of accessory thyroid glands which he frequently finds at the base of the tongue and which he classified as the superior group. He records

[1] *Centralb. f. allg. Path. u. path. Anat.*, 1903, xiv, 84.
[2] *Jour. of the Amer. Med. Assoc.*, 1905, xlv, 1854.

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39 cases. In only three is there a note upon the histology of the tumor. Two presented the appearance of "normal thyroid," and one of "colloid goitre." In six, or 15 per cent of the cases, there was recurrence after removal but no other signs of malignancy.

Third, *Propagation of bits of thyroid tissue through the circulatory system.* It is a well-known fact that certain tissues, especially young embryonal cartilage, when transplanted into different tissues of the body or when injected into the circulatory apparatus are apparently nourished and in certain instances continue to grow. An apparently analogous condition is true in regard to the thyroid-gland tissue. Portions of this gland have been excised and immediately transplanted into another animal of a foreign species. The tissue not only has remained alive but has apparently continued to produce its normal secretion. Although no proof is at hand, it is possible that these metastatic tumors could result from small particles of thyroid tissues which had found their way into the circulatory apparatus and had been transferred to distant portions of the body. In an organ as vascular as the thyroid such a condition is not inconceivable, especially under conditions of trauma.

As is well known metastases from tumors of the thyroid, like those of the prostate, occur most commonly in bony structures.

VI.—Exophthalmic Hypertrophy. Six Cases. All Females.

No.	Age of onset.	Age at operation.	Duration.
1	28	29	16 months.
2	25	26	1 year.
3	20	21	1 year.
4	24	27	3 years.
5	28	43	15 years.
6	44	46	2 years.

Average age of onset, 28; average age at operation, 32; average duration of disease, 3 years and 10 months.

Result.—In two cases death occurred, one (case No. 3) on the table at the end of operation as a result of the anæsthetic; the other (case No. 2) died seven days after operation, with the symptoms of extreme hyperthyroidization. The remaining four cases have been either entirely cured or greatly benefited by the operation. Case No. 1, four years after operation, is well and

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all the symptoms have been relieved except slight prominence of the eyes which remains. The portion of the gland that was left at operation is now distinctly palpable. Case No. 4, one year and two months after operation: the symptoms are all relieved and the patient is able to pursue his work. Before operation exophthalmus, tachycardia and nervousness were marked. Case No. 5 is well ten months after operation. Case No. 6: operation was done but one month ago. The condition of the patient is improved.

CASE XVIII.—(Path. No. 64–25.) Female, married, aged 26. Complains of enlargement of neck, poor sight and some difficulty in breathing. Onset one year ago; first symptom enlargement, followed by exophthalmus. Thyroid gland now presents symmetrical enlargement; exophthalmus very pronounced, marked tremor of hands. Systolic murmur heard over base of heart; not transmitted. Heart not enlarged. Pulse 140.

Operation, June 24, 1903, by Dr. A. Vander Veer. Ether anæsthesia. Both right and left lobes were removed. For three or four days after operation the pulse ranged between 130 and 158, temperature between 100 and 102° F. Delirious at intervals. Death on the seventh day.

Pathology.—The gross description merely contains the statement that the specimen consisted of two masses of glandular tissue, one measuring 8x4x2 cm. and the other 5x4x1.5 cm.

Microscopic Examination.—(See Fig. 3.) Sections 1, 2 and 3 all show the lobulated structure of the thyroid gland. There is an increase in the interlobular connective tissue. The vesicles composing the lobules are very irregular in size and shape. The colloid material in many of the vesicles has been entirely replaced by epithelial cells. Instead of a single layer of epithelium lining the individual vesicles, we see a number of layers, this proliferation of cells often producing invaginations or papillary projections into the cavity of the vesicle. In certain areas this proliferation of cells has advanced to such an extent as to completely fill the vesicle and we have entire lobules presenting a solid cellular structure. The cells are of a high columnar type. There is lymphocytic infiltration in areas.

Microscopic Diagnosis.—Advanced and diffuse exophthalmic hypertrophy.

CASE XIX.—(Path. No. 763.) Female, single, aged 21. Enlargement of thyroid for one year, more marked on right side. Exophthalmus, tremor and tachycardia pronounced. As patient steadily grew worse under medical treatment, operation was advised.

Operation, September 28, 1904, by Dr. Elting. Ether anæsthesia. Excision of right lobe and isthmus. Left lobe not removed. The patient died on the table at the end of operation.

Pathology.—Macroscopic Examination: Specimen consists of two pieces of tissue, measuring respectively 6x4.5x3 cm. and 3x2.5x2 cm. in size. Both are of similar structure. The larger is somewhat lobulated and is encapsulated except on one surface, near the upper pole, where there is

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a raw granular surface corresponding in diameter to the smaller piece. Both masses are more or less nodular and on section have a pinkish white granular appearance. There are several cysts 0.5 to 1 cm. in diameter containing straw-colored grumous fluid. The surface presents rather round or oval areas, each being somewhat distinct from the other.

Microscopic Examination.—The sections present an unusual picture for exophthalmic hypertrophy. They have in general a definite lobulated glandular appearance. In many lobules the proliferation of epithelial cells has progressed to such an extent as to entirely obliterate the characteristic thyroid gland structure, giving solid epithelial masses. The walls of the individual vesicles have disappeared, evidently as a result of pressure. In one such area (see Fig. 4) there is in addition an unusual change in the cell morphology. As seen in the microscopic drawing, the cells are very large and irregular in shape and in this regard suggest very strongly malignant transformation. In one section, evidently representing the wall of the small cyst mentioned above, the hypertrophy is not so far advanced and hyperplasia of the cells with papillary projection or invagination of the epithelial layers into the cavity of the vesicle is seen, representing more the picture we recognize as that of exophthalmic hypertrophy. The colloid material except in a few places has disappeared. In the study of these sections one is impressed with the possibility of the association of exophthalmic hypertrophy and carcinoma.

Case XX.—(Path. No. 05-1376.) Female, single, aged 46. For six years headache, extreme nervousness and dizziness at irregular intervals. Two years ago onset of exophthalmus, tachycardia and tremor. Four months later observed enlargement of thyroid gland. This enlargement is symmetrical and well marked.

Note on physical examination.—Patient is a rather slightly built woman, rather poorly nourished and anæmic. Areas of discoloration of skin on left cheek and backs of both hands. Exophthalmus definite but not of an extreme degree. Sight has failed rapidly. Pulse regular, of even tension, 96 per minute. On admission to hospital it is recorded as 90. Thyroid gland shows a nearly symmetrical enlargement, left lobe a little larger than the right, measuring about 8.5x5 cm. and is moderately firm.

Operation, December 29, 1905, by Dr. Elting. Ether; excision of left lobe and isthmus.

Pathology.—Macroscopic Examination: Specimen consists of what is apparently the left lobe and a portion of the isthmus of the thyroid gland, which have been removed in one piece. The outer surface has a pinkish-yellow mottled appearance. It is covered by a rather delicate fibrous capsule, which has been torn in places and adheres by firm hair-like adhesions. The surface has a distinct lobulated appearance, the lobules varying in size from 0.5 to 2 cm. Several minute cysts 1 to 2 mm. in diameter are seen upon the surface. The tissue has a rather firm feel, and is very nodular. Section has been made through one area where near the surface a cyst has been opened. This cyst is 1.5 cm. in diameter and contains some thick, viscid, translucent material. On section the cut surface presents a reddish-yellow mottled appearance. Lobulations are definitely seen. These vary in size from 1 mm. to 1 cm. and are of

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Plate V.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

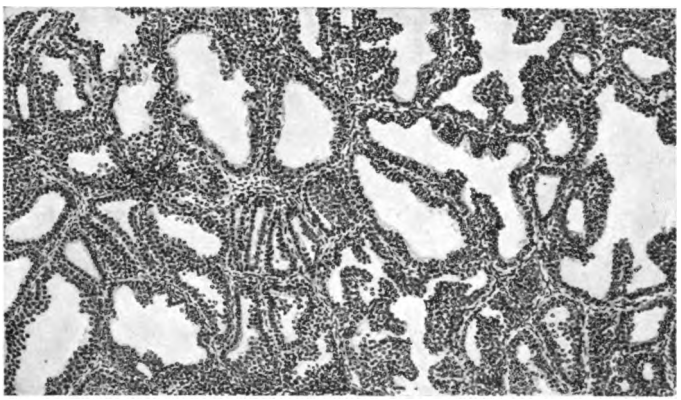

Fig. 3.—Microscopic drawing of an exophthalmic hypertrophy (exophthalmic goitre), 4 oc., 3 obj., Leitz.

In this drawing the hypertrophy is indicated by the proliferation of the epithelial cells lining the vesicles and the papillary projections into their lumen. In places some of the vesicles have been compressed by the hypertrophy of the surrounding epithelium.

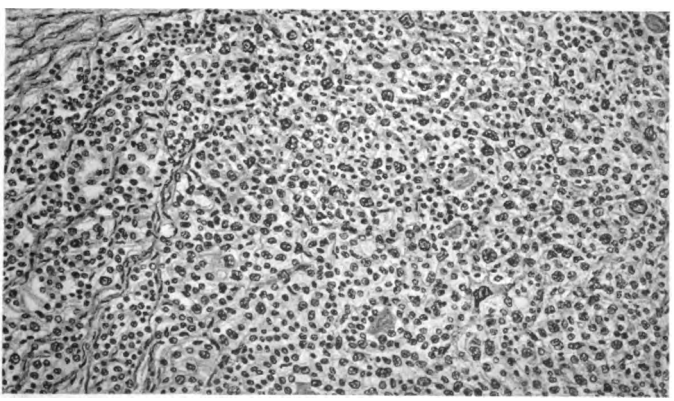

Fig. 4.—Microscopic drawing of a section of thyroid which presents in other areas a definite picture of exophthalmic hypertrophy, 4 oc., 3 obj., Leitz.

(See microscopic description.)

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widely different shape. The connective-tissue surrounding the lobules can be seen as distinct white bands. It seems more abundant near the center and in the posterior part. Within the lobules can be seen minute translucent areas, which presumably are thyroid vesicles filled with colloid. The entire lobe as far as determined by section has this appearance. In the isthmus are areas of a more distinct red appearance. The lobules are firm and definite translucent areas cannot be seen. The appearance here approaches more nearly that of normal thyroid tissue.

Microscopic Examination.—A series of sections show two definite processes. There is seen to be in the majority of the sections a marked increase in the size of the alveoli and in the amount of colloid present. In certain lobules this is much more pronounced, and suggests a simple hypertrophy, differing perhaps only in the tendency of the cells to assume a higher type in many of these large colloid alveoli. In other areas there is cellular proliferation with diminution or disappearance of the colloid material. The increase in the number of epithelial cells is very great while their approach to the columnar type is not so marked. An alveolar arrangement is frequently difficult to make out. Section through the wall of the small cyst, noted above, shows it to be in the center of a minute encapsulated adenoma. The connective tissue of the gland is moderately increased in amount and there is considerable lymphocytic infiltration in areas.

It seems, then, that we may recognize two forms of exophthalmic hyperthrophy; in the one form the disease begins in an apparently normal gland and the process is symmetrical, so that histologically we find everywhere the type of lesion so well illustrated in Fig. 3. Clinically in this form we recognize as a rule a very symmetrical enlargement of the gland, though one which never attains great size. The disease is of comparatively short duration, patients dying as a rule in from one to three years if untreated. The well known symptom-complex of the disease,—enlargement of the gland with exophthalmus, tachycardia and tremor,—is invariably present. In the other form the exophthalmic process is secondary or associated with some other type of thyroid affection. In three, or one-half, the cases in this series an associated simple colloid hypertrophy was found. The cases in this series illustrating this type are Nos. 4, 5 and 6.

This form is characterized clinically by a longer duration, by a greater increase in the size of the gland, and by lesser severity of the symptoms. These cases, however, all had exophthalmus, tachycardia and nervousness of greater or lesser severity. In Case V, while the enlargement of the gland was of 15 years' duration, the symptoms of exophthalmic goitre had developed more

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recently. In the other two cases these symptoms were present from the onset.

The histologic picture also differs. Instead of a uniform process, as in the former group, we see the exophthalmic hypertrophy only in foci or in various lobules scattered throughout the gland. In the cases where this hypertrophy is observed it is of a lesser degree. Other investigators have also recently called attention to the fact that exophthalmic hypertrophy is frequently associated with various pathologic conditions of the thyroid, as cysts, adenomata and carcinomata, and that these may be the unproduced atypical exophthalmic goitre symptoms. Usually there is present the nervousness, tachycardia and tremor of varying degree while the symptoms of exophthalmus may be wanting.

In typical cases of exophthalmic goitre, which present the well-known symptom-complex, all writers agree that the histologic changes found in the gland are definite and constant. They have been characterized as a true hypertrophy. They very closely resemble the compensatory hypertrophy which is seen in the remaining portion of the thyroid gland after its partial excision, and which in this manner has been so frequently produced experimentally in dogs. Briefly the changes are (1) a change of the epithelium from a low or cuboidal type to a high cylindrical form, (2) a gradual disappearance of the colloid material which seems to be one of the earliest evidences of beginning hypertrophy, (3) alteration in the size and form of the alveoli due to the hyperplasia and infolding of the epithelium, (4) increase in the vascular supply and in the connective tissue stroma.

As we have noted, however, in cases in which symptoms are atypical no such definite changes are observed. We may see only in foci evidences of this process. It may amount simply to a change in the size and form of the cell, and perhaps instead of a single layer of epithelium lining the alveolus there may be two or more. There may be said to be, however, in all cases evidence of proliferation of cells with increased activity. Whether or not we shall be eventually forced to the conclusion that all the various affections of the thyroid gland characterized by cellular proliferation give rise to the symptoms, more or less complete, of Graves' disease is a matter which requires further study.

As to the pathogenesis of this affection nothing can be said to have been as yet definitely established. The main dispute is still whether the disease is of nervous origin or has its basis in an

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abnormal condition of the gland itself. The majority accept the latter view, and hold that the disease is a manifestation of an excessive or perverted secretion of the thyroid epithelium. This seems the most rational supposition and it is borne out by certain facts,—viz., the similarity in the histology of the compensatory hypertrophy and the exophthalmic variety; the relationship between the advancement of the hypertrophy and the duration and severity of the clinical symptoms; and the beneficial effects that are produced by removal of a portion of the hypertrophied gland. What relation if any the parathyroids have to exophthalmic goitre has not been determined. In none of these cases were these bodies examined. The changes that have been described are not at all constant.

In regard to the age of onset, the cases of this series correspond closely with those of other observers. By far the greatest number appear between the ages of 20 and 30, five out of six cases are recorded above. In one case, however, the age of onset was stated as 44. An onset before puberty or after 40 is rare. The disease is much more common in females than males, the proportion as variously stated ranging from 3 to 1 to 17 to 1.

VII.—Chronic Thyroiditis. One Case.

Case XXI.—(Autopsy No. 0-283.) Autopsy, April 18, 1900, by Dr. Blumer. Female, aged 40. No clinical history.

Anatomical Diagnosis.—Sclerodema with pigmentation of the skin affecting the face, posterior part of the trunk and extremities. Acute serofibrinous pericarditis, with acute myocarditis and diffuse interstitial myocarditis. Double hydrothorax with acute fibrinous pleurisy on the left side. Acute bronchitis with emphysema of the lungs and atelectasis of the lower lobes. Chronic passive congestion of the liver. Acute infectious nephritis. Chronic interstitial thyroiditis. Chronic interstitial mastitis. Tuberculosis of a bronchial lymph-gland. Small ulcers over the internal condyles of the humeri.

Pathology.—Macroscopic Examination: The thyroid gland is small, firmer and somewhat grayer in color than normal. It contains apparently an increased amount of connective tissue.

Microscopic Examination.—Marked changes in the gland are seen. These take the form of a great increase in the interstitial tissue of the organ, producing compression and atrophy of the glandular substance. The new-formed connective tissue is mostly in the form of a dense, fully-formed fibrous tissue, but there are areas in which the thyroid tissue is infiltrated with small, round, lymphoid cells, apparently representing a recent infiltration. There is an increase in the elastic tissue. The gland substance shows varying degrees of compression. In some places it has almost entirely disappeared over quite wide areas; in other places it is

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apparently but little affected. There is an abundance of colloid material in the slightly affected areas.

Microscopic Diagnosis.—Chronic interstitial thyroiditis.

This case is not introduced into this series to raise the question of the relation of the thyroid to the condition of scleroderma, but as a typical illustration of the pathologic changes produced in the gland by a chronic inflammatory process. Acute inflammation of the thyroid gland frequently occurs following acute general infections, as typhoid and the exanthemata. The chronic form is very often associated with other thyroid affections, the hypertrophies, cysts and tumors, and they present in varying degrees the condition here described.

VIII.—Tuberculosis. Two Cases. One Male, One Female.

No.	Age of onset.	Age at operation.	Duration.
1.....	40	42	2 years.
2.....	35	43	8 years.

In the first case the previous health of the patient was said to have been good, but death from pulmonary tuberculosis occurred six years after the operation. In the second case the history at about the time of the onset of the thyroid involvement suggested pulmonary tuberculosis. The patient now (two years after operation) is in good health and presents no evidences of active tuberculous disease in any organ.

Case XXII.—(Path. No. 64–2.) This case I am able to report as tuberculosis of the thyroid only upon clinical evidence, as although the microscopic sections show tuberculosis granulation tissue no thyroid structure can be made out. The patient was a male, aged 42. The disease began two years before with a small "lump" in the region of the thyroid gland which gradually increased to the size of a walnut, suppurated and discharged spontaneously, leaving two small sinuses which have persisted for a year. At the operation by Dr. Macdonald the sinus tracts were found to lead down to the thyroid gland and they were excised together with the gland in one mass. Clinically, as recently related to me by the operator, the process had its origin in the thyroid gland.

Pathology.—Macroscopic Examination: The specimen consists of a piece of tissue about one-half the size of a hen's egg. It contains some tissue which is presumably thyroid gland, and leading into it from the surface of the specimen are two sinus tracts, the walls of which are extremely ragged and lined with yellowish purulent material. *Bacteriologic examination* fails to show tubercle bacilli.

Microscopic Examination.—No thyroid tissue is to be seen. The sec-

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Plate VI.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

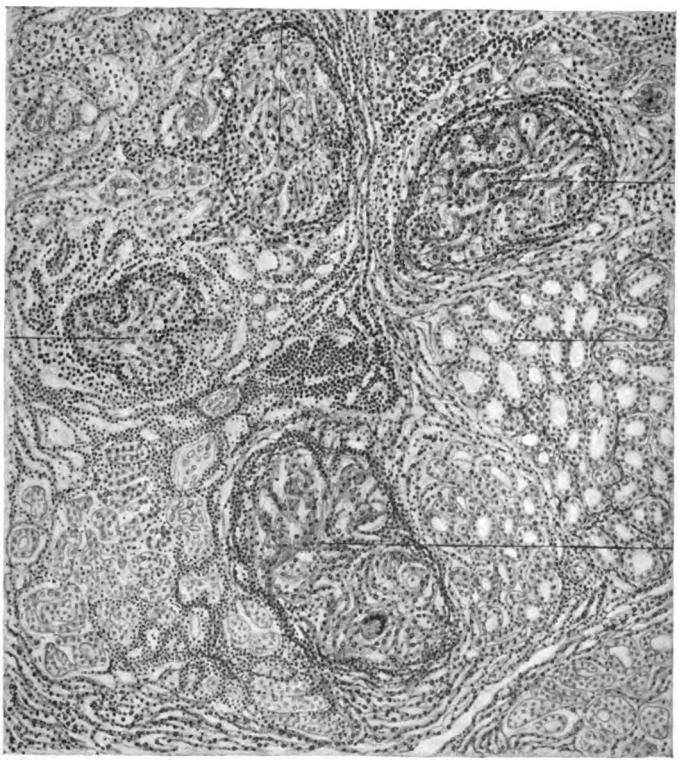

Fig. 5.—Microscopic drawing of tuberculosis of the thyroid gland. 4 oc., 3 obj., Leitz. (a) Tubercles, in the lower one of which is seen a giant cell. In the centre of the drawing, between the tubercles, is an area of lymphocytic infiltration. (b) Normal thyroid tissue.

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tion consists of connective tissue and of large areas of caseation. Surrounding these areas of caseation is typical tuberculous granulation-tissue, made up of epithelioid and lymphoid cells, and containing an occasional giant cell.

CASE XXIII.—(Path. No. 64-21. History taken and physical examination made December, 1905, two years after operation.) Female, aged 45. When 14 years of age parents thought she had consumption; but, if so, she recovered completely. She married at 21 and now has 7 children, all in good health. At birth of last child, 11 years ago, she had puerperal fever and was seven months in bed. After this had a severe cough, night sweats and considerable expectoration. During this illness her physician first noticed a small tumor in the median line of the neck in the region of the thyroid gland which gradually increased till two years ago, when it reached the size of a hen's egg. It was tender on pressure and sometims painful and caused some dyspnœa during the last year before operation. It never showed redness or signs of inflammation. The patient entered hospital at this time for an operation for uterine myomata and she was persuaded by the surgeon to allow removal of this enlarged portion of thyroid.

Operation, November 5, 1903, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of reddish brown tissue 6x4x2.5 cm., in which lies a sausage-like mass. This latter on section is found to be of a uniform consistency and of moderate firmness. Color is slate brown and deviating striæ give to the cut surface a lobulated appearance.

Microscopic Examination.—(See Fig. 5.) The thyroid tissue shows marked proliferation of alveoli, the majority of which are massed together, making the outlines of individual alveoli indistinct, while others contain a moderate amount of colloid material. In many of the lobules are circumscribed masses of epithelioid cells with occasional giant cells and a peripheral ring of lymphocytic infiltration. But a few of the tubercles show early caseation.

Microscopic Diagnosis.—Tuberculosis of the thyroid gland.

The patient was seen in December, 1905, 2 years after operation and this note on her present condition was made: "Patient is fairly well nourished, but slightly anæmic. There is a linear scar in the median line of neck 7.5 cm. in length, extending from a little beneath the chin to the episternal notch. Aside from a little thickening and redness at its lower end the scar appears healthy. There is no apparent enlargement of any portion of the thyroid gland. Patient has no cough and states that she is in good health and able to pursue her work. Examination of the lungs reveals no evidence of disease, though the breath sounds at both apices and considerably subdued. There is no glandular enlargement anywhere."

While it is true that tuberculosis of the thyroid gland is a rare disease, from recent studies it has been demonstrated that it is not so rare as was formerly supposed. Thus P. Bruns[1] in his

[1] *Beitrage zur klin. Chir.*, 1897, xi.

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report of 100 postmortem examinations made by Chiari of persons who had suffered from tuberculosis, states that the thyroid gland was involved in seven. Of these cases 96 had suffered from chronic pulmonary tuberculosis, and in only four of these was the thyroid gland involved; the other four were cases of acute miliary tuberculosis, and in three of these the gland showed involvement. Weigert in fifty cases of chronic pulmonary tuberculosis found tuberculosis of the thyroid in six. Two forms of involvement are recognized; a miliary form secondary to a general miliary tuberculosis, and a nodular form affecting the gland diffusely. The former is the more common. It does not produce any enlargement of the organ as a rule. Of the nodular form Bruns was able to collect six cases besides his own; in three of these from a clinical point of view the thyroid lesions were primary. This form is attended by enlargement of the organ sometimes sufficient to produce pressure symptoms. As illustrated in Fig. V, these tubercules have the ordinary characteristics of tubercles in other organs. They probably always arise in the interstitial connective tissue separating the vesicles.

In the first case here recorded the data is so incomplete that no definite conclusions can be drawn. The clinical history states that the patient's previous health had been excellent, but there is no record of a physcal examination to exclude a possible pulmonary involvement. Then the fact that he is said to have died four years later of pulmonary tuberculosis leaves us in doubt as to whether the disease was primary in the thyroid with secondary involvement of the lungs or *vice versa*.

W. B. Stanton[1] has recently made the important observation that in a comparatvely large number of cases of pulmonary tuberculosis there were symptoms more or less complete of exophthalmic goitre and in these cases he has been led to examine the thyroid glands. The report is only a preliminary one and no cases in which he has observed these symptoms have died. He could not therefore give the results of histologic examination. Clinically there was slight thyroid enlargement. He records 26 cases of pulmonary tuberculosis aside from the above in which the thyroids were examined postmortem, but in which the patients were not examined clinically for those signs. In these, tubercles were found in four. As serial sections were not made he thinks it probable that the proportion found to contain tubercles is much

[1]American Medicine, 1905, x, 605.

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too small. Further investigation of this point might yield informaton of great value.

IX.—Carcinoma. One Case.

Case XXIV.—(Path. No. 98-43.) Female, aged 36, with history of illness for last three years. Prominent symptoms are enlargement of thyroid gland, with pain and anæmia. The patient was operated upon two years ago for thyroid enlargement, but no pathologic study of this specimen was made.

Second operation by Dr. A. Vander Veer, February 18, 1899.

Pathology.—Macroscopic Examination: Specimen consists of six masses of tissue, all roughly lobulated and varying in size from 6 to 3 cm. in greatest diameter. They all present similar appearances and are not distinctly encapsulated, though portions of capsule are here and there evident. Where a capsule is present it is generally smooth and of a yellowish-red color. The portions of the growth which are uncovered by capsule are finely lobulated, of a light yellowish-brown color, and have a translucent appearance. This appearance suggests, in some places, the appearance of thyroid-gland tissue; in other places it has a myxomatous character. On section the nodules differ in appearance; the smaller and presumably the younger ones have an almost homogeneous yellowish-gray cut surface, which is covered by sticky mucilaginous fluid which has the glistening appearance of mucoid tissue. In one or two of the smaller masses are areas of hæmorrhage. In one rather large area of light reddish-brown tissue which does not look like hæmorrhage, there is an area homogeneous in character and slightly granular. In two of the largest nodules near the center are areas of necrosis and calcification.

Microscopic Examination.—Sections from two different portions show an adenomatous tissue divided into irregular lobules by rather dense fibrous connective-tissue septa, which extend inward from a capsule which is present at one side. Except in a few small lobules near the periphery, where characteristic colloid-containing vesicles are seen, the tissue could not be recognized as thyroid-gland tissue. It is composed of papillomatous-like projections and long epithelial tubules with cavities of thyroid-gland spaces. This arrangement becomes complex and branching as the process develops, until they finally fill up the cavities, producing a gland-like appearance. The epithelium rests upon no visible basement-membrane; the stroma is very scanty. In the connective-tissue septa are many solid epithelial clumps which probably represent new foci of growth.

A section from the homogeneous mass differs only in that no connective-tissue septa are seen, and the spaces are more closely packed with epithelial cells. This section also shows acute inflammation. The epithelial cell is of a high cylindrical type, varying greatly in size and shape.

Microscopic Diagnosis.—Adeno-carcinoma of thyroid gland.

From one observation of carcinoma of the thyroid no important deductions can be made except to call attention to its relative infrequency. One case in 61 thyroid affections, as indicated by

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this series is, however, undoubtedly too low a proportion and not borne out by the statistics from other sources. Bloodgood[1] in exactly twice the number of cases records seven of carcinoma. The most elaborate study of this condition that has appeared is by Ehrhardt,[2] who has collected 150 cases of carcinoma. Sixty-five of these occurred in men and eighty-five in women; 111 appeared between the ages of thirty and sixty. In over 50 per cent. of these cases it was definitely stated that a simple goitre preceded the development of the carcinoma, and in only a comparatively small number that it arose in a normal thyroid. This is the reverse of the condition seen in this country, probably due to the fact that we have no "goitrous districts," Ehrhardt recognizes three main varieties,—the medullary, which is the most frequent, the adeno-carcinoma, and the scirrhus. The latter is, in his experience, rare. Metastases occur early as a rule. In ninety-four bodies examined metastases were found in all but fourteen. In forty-six cases twenty-three had metastasized by the bloodstream alone, nine by the lymphatics alone, and fourteen by both these channels. As to the location of metastases, the lungs and bones are the most frequent seats. The bones of the skull and inferior maxilla are most commonly involved, though the sternum and long-pipe bones do not escape.

The average duration is about two years, the scirrhus form being the most chronic.

Clinical Diagnosis of Thyroid Affections.—When we bear in mind that the symmetrical enlargement of the thyroid gland indicates a hypertrophy, and the asymmetrical a tumor or a cyst, we have gone a great way towards making a diagnosis. To characterize all of the enlargements of the thyroid as "goitre" is obviously improper, as it conveys no intelligent clinical or pathologic meaning. If this term is used, it should apply to the hypertrophies, and we can then properly speak of the simple goitre and the exophthalmic goitre. To differentiate these latter conditions clinically is not difficult, for in exophthalmic goitre the subjective symptoms are definite and constant. In the simple form the rule is a much greater increase in the size of the gland but no symptoms except those produced locally by pressure. The age of onset and the duration of the disease are also important aids in diagnosis, as has been shown in the preceding tables. In

[1] *Surgery, Gynecology and Obstetrics*, 1905, i, 113.
[2] *Beiträge zür klin. Chir.*, 1902, xxxv 343.

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the simple hypertrophy the age of onset in a large proportion of cases is before twenty. In an accurately recorded history I believe it would be exceptional to establish an onset after twenty-five. In the exophthalmic variety an onset before twenty is extremely rare; the majority of cases appear between the ages of twenty and thirty. The duration of the disease in the simple form is much longer, often twenty or thirty years, while that of the exophthalmic hypertrophy is usually less than two years. Where these two conditions are associated, or where the exophthalmic hypertrophy appears secondary to other thyroid affections, greater variation in these respects is seen. We must bear in mind that in either form of hypertrophy the process in one lobe may have advanced further than in the other, producing an asymmetrical enlargement, but on the other hand no part of the gland appears normal. In other words the process is a diffuse but not always an uniform one. Again, we have seen in certain cases a fairly symmetrical enlargement produced by an adenoma or cyst in either lateral lobe. These multiple tumors are comparatively rare, however, and on close examination present distinctive features. Of the tumors, the cysts and the adenomata are the most frequent, and they are often very difficult to differentiate. They both present the features of encapsulated tumors. The cysts are more apt to be smooth and ovoid in shape, while definite lobulations can often be made out in the adenomata. Variation in the size of the tumor seems to be frequent in the case of cysts. In regard to the recurrent adenomata, two of our observations at least would point to their being of a mild type of malignancy. Considering the long duration, however, and the fact that no metastases occurred, they do not present the features of carcinoma of the thyroid. In one case a secondary growth appeared in the region of the primary one.

From the fact that metastases of the thyroid tissue occurs in cases in which no primary tumors of the gland has been noted, bone tumors looked upon as primary should be approached with this possibility in mind.

Early diagnosis of the carcinomata presents the greatest difficulties and obviously is of the greatest importance. Age here is to be considered as indicated by the statistics of Ehrhardt. The disease is usually of short duration, a few months to one or two years. As met with in this country, carcinoma of the thyroid does not produce a large tumor, but it rapidly infiltrates the gland

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and surrounding tissue and dyspnœa and dysphagia are early symptoms and out of proportion to the size of the growth. Change in the voice is also an early observation (Bloodgood). In districts where simple hypertrophy is endemic a very large proportion of the cases of carcinoma, as recorded by Ehrhardt, are secondary to this condition. Here the important feature is a sudden increase in size in the hypertrophied organ, with the return of symptoms after a quiescence of perhaps many years. Primary sarcoma of the thyroid is a rare affection and as no cases were observed in our series the condition will not be discussed.[1]

Treatment.—As the symptoms in the uncomplicated cases of simple hypertrophy and benign tumors are of a mechanical nature, the severity of these symptoms has been our guide in treatment. Rarely is operation undertaken for the relief of the deformity alone. I believe, however, that since so large a number of these cases undergo secondary changes in later life, making operation imperative, that they should be considered upon the same basis as similar lesions in other organs. In the case of the tumors and cysts an early operation is advocated. With the simple hypertrophy, if the patient has passed young adult life, the period when we might expect a subsidence of the process, and the gland continues to enlarge, a portion of it should be removed. If after a quiescent period new growth is observed, operation may be necessary for the relief of urgent pressure symptoms, and here, too, carcinoma must be considered. Scarcely fifty years have passed since Dieffenbach considered thyroidectomy a rash undertaking. To Kocher more than anyone else is due the credit of the advances in this field of surgery. At the German Surgical Congress, in 1900,[2] he reported the results of his second thousand cases of thyroidectomy, of which 929 were upon cases of simple hypertrophy and benign tumor. He had only four deaths, giving a mortality of 0.4 of 1 per cent. The greatest single factor contributing to this low mortality-rate was undoubtedly the substitution of local for general anæsthesia.

The general principles which guide us in the treatment of carcinoma of other organs should apply here, remembering that metastases occur early. Operation to effect a cure must be un-

[1] For report of cases and statistics see Lartigau (*Amer. Jour. Med. Sciences*, 1901, cxxii, 156).

[2] *Archiv. für klin. Chir.*, 1900, lxiv, 454.

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dertaken before there is extensive invasion of the surrounding tissues.

In the treatment of exophthalmic goitre the various drugs and methods employed are almost innumerable. The weight of opinion now seems to favor partial thyroidectomy, and I believe justly so, for with the accumulating statistics the percentage of cures is increasing and the number of primary deaths decreasing. No other form of treatment has offered so much hope. The observations in this series have been made entirely on the operative treatment, but to give an opportunity for comparison I may be allowed to quote from a review of the literature made recently by the writer,[1] in which the results of some of the other more recent methods of treatment are recorded. In late years attempts have been made in many German clinics to develop a specific treatment of exophthalmic goitre. Lanz,[2] as early as 1894, began the use of the milk of thyroidectomized goats in patients with Graves's disease. He has recently recorded favorable results in five cases. Burghart and Blumenthal[3] in Leyden's clinic have injected the blood-serum of amyxo-œdematous patients into those suffering from exophthalmic goitre. Leyden reviews their results and thinks they are encouraging. Later, in this clinic, was introduced the use of a precipitate from the milk of thyroidectomized goats, called "rodagin." A few cases are recorded of slight improvement after continued use of this substance. Kollaritis reports no improvement in three cases in which he employed this method.

Moebius and Schultes[4] have used the serum of thyroidectomized sheep. This serum is called *antithyroidin.* Moebius reports three cases somewhat improved by this treatment and later two other cases which were benefited. Schultes and Rosenfield have likewise each reported a case. In a recent communication Moebius[5] speaks rather guardedly of the employment of this serum. Kuh,[6] after treating eleven cases with the serum, is unwilling to make any statement as to its curative effect. He thinks it relieved nervousness and diminished tachycardia.

In regard to the operative treatment, in four of our six cases

[1] *Albany Med. Annals*, 1906, xxvii, 111.
[2] *Münch. med. Wochenschr.*, 1903, 1, 146.
[3] *Deutsche med. Wochenschr.*, 1899, xxv, 627.
[4] *Münch. med. Wochenschr.*, 1901, xviii, 1873.
[5] *Münch. med. Wochenschr.*, 1903, 1, 146.
[6] *Medicine*, 1905, xi, 672.

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the partial excision of the thyroid gland has been attended with excellent results. In two of these all the symptoms have been relieved; in one the operation was of too recent date to determine the ultimate result, but the symptoms one month after operation improved in all respects; in the other all the symptoms except exophthalmus had disappeared, and the patient is able to pursue her work. The time now intervening since operation varies from one month to four years, as shown in the table. Of the two deaths one could be ascribed to the anæsthetic, and the other, in which death took place on the eighth day with the symptoms of extreme hyperthyroidization, as a late case probably beyond possible recovery. It should be borne in mind that the operative treatment, to be of the most value, should be undertaken early, before damage has been done to the nervous system. In this condition even more than in other forms of thyroid affections, the importance of local anæsthesia cannot be too highly estimated. As further proof of the superiority of the operative treatment, the statistics of a number of observers are quoted. The best results of partial thyroidectomy yet published are those of Kocher—59 cases: 75 per cent. cured; 17 per cent. improved; 6.7 per cent. dead.

At the last German Surgical Congress, April, 1905, Friedheim from the clinic of Kümmel reported the results of twenty cases of partial thyroidectomy after five or more years had elapsed. Fourteen were cured, two much improved, three slightly improved, and one had died. In seven of the cured cases the operation had been performed nine or more years previous; in one, fifteen and a half years. He further presents the statistics of the other large German clinics for the last years as follows:

	Cases.	Cured.	Improved.	Dead.
Von Mikulicz	18	10	7	1
Krönlein	24	16	6	2
Kocher	59	45	10	4
König	8	4	..	1

Summary.

In the study of this series of cases especial emphasis is directed to the following points:

I. Simple colloid hypertrophy is the most common affection of the thyroid gland. In a large percentage of cases this hypertrophy is temporary, representing, apparently, a physiological

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process, taking place in early adult life, and later there is a return of the gland to its normal condition. This early hypertrophy may be permanent, and in addition there may be a return of the secretory activity of the cells together with the formation of new thyroid tissue. This latter process often simulates clinically a malignant transformation.

II. Adenoma of the thyroid is by no means a rare affection. Its differentiation from simple colloid hypertrophy is readily made, both from a clinical point of view and from a macroscopic examination of the specimen. While the histologic structure of the two lesions are similar, careful examination reveals determining points of difference. The various types of adenomata, differ only from a histologic standpoint; this difference being due entirely to the secretory activity of the cells of the individual vesicles. The ademonata may occur singly or as multiple tumors of one or both lobes. Recurrence after removal is occasionally observed in tumors which from a histologic point of view, at least, are adenomata.

III. Hæmorrhage as a true etiologic factor in the production of cysts of the thyroid gland, is uncommon. By far the greatest number of cysts of the thyroid are produced by a degeneration of adenomata. The walls of these cysts we find composed of a histologic structure which exactly corresponds to one or the other of the types of adenoma. Secondary changes in the cyst walls are common, and are the result of compression and degeneration.

IV. Thyroid tumors may occur, which histologically present none of the indications of malignancy, but which clinically must be considered as such. These tumors occur outside of the thyroid gland, are probably metastatic, and usually appear in bony structures, the gland itself presenting at least no clinical evidence of primary involvement.

V. In exophthalmic goitre in addition to the type of the disease which presents a definite and constant clinical and pathological picture, there are other, so-called, irregular forms, which are associated with or occur secondarily to other thyroid affections, in which the symptom complex of Graves's disease is not complete, and the epithelial hyperplasia occurs only in foci and is of lesser degree.

VI. Tuberculosis of the thyroid, while a rare affection, is a possibility which must always be considered in diagnosis. The disease may occur in one lobe without involvement of the others,

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and produce a tumor which clinically simulates an adenoma, and the condition though of long standing may present no visible indications of an inflammatory condition.

VII. Carcinoma of the thyroid is more common than indicated by this series. Outside of the "goitrous districts" carcinoma occurs most often in glands that are apparently normal, and here the type of growth is that of an adeno-carcinoma.

VIII. The diagnosis of the benign thyroid affections should as a rule present little difficulty. In contradistinction to the benign lesions carcinoma does not produce a large tumor and obstructive symptoms and infiltration of the surrounding tissues occur early.

IX. The treatment of thyroid lesions with the possible exception of exophthalmic hypertrophy rests entirely upon a surgical basis. Accumulating experience likewise tends to emphasize the superiority of partial thyroidectomy over the many other methods employed in the treatment of exophthalmic hypertrophy.

X. The risks of general anæsthesia are too great to commend its employment as a routine practice in operations upon the thyroid gland. All cases can be successfully dealt with under local anæsthesia, and the primary death rate reduced thereby greatly.

PUERPERAL INFECTION: REPORT OF SIX CASES ILLUSTRATING ITS VARIED CHARACTER.*

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Puerperal infection, in spite of the increase in our knowledge of prophylaxis, is still the cause of the majority of deaths occurring in pregnancy and the puerperium, and remains, therefore, one of the most frequently discussed topics in obstetric literature. Although the pathology of the simpler or so-called "pure" forms of infection have been thoroughly described, the varied manner in which the disease may manifest itself has not been so generally understood. It seems, therefore, justifiable to add, to a subject of such perennial interest, a report of several cases studied both clinically and pathologically.

Puerperal infection differs from all other bacterial infections

* Published also in *American Medicine* 1906, xi, 231.

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in that it occurs in organs whose anatomic relations and blood supply have been altered temporarily. This is of as great importance in determining the extension of the infection as is trauma in favoring the original infection. Autoinfection is to be considered also, not only as infection from organisms existing in some part of the genital canal, but also as infection which may be carried to the genitalia from some preexisting focus in a remote part of the body. Two cases of autoinfection from foci outside the genitalia are here reported. Intercurrent bacterial disease primarily nongenital must also be considered a factor in the causation of puerperal infection.

A few words concerning terminology may not be out of place, for the obstetrician is notoriously lax in his use of terms, *e. g.*, the frequent use of the term septicemia when only a toxemia exists.

In any discussion of infection we must consider on the one hand the local lesion and on the other the secondary manifestations. The local lesion is due to the toxic substance elaborated by microorganisms at the point of invasion; at the same time, these soluble substances pass into the general circulation and cause constitutional symptoms. The local lesion may be an abscess, a urethritis, or a pneumonia, etc.; in puerperal infection it is usually an endometritis. The constitutional symptoms constitute a toxemia and not a septicemia. The latter results only when the microorganisms themselves enter the blood stream and are distributed to all parts of the body. Needless to say an absolute diagnosis between toxemia and septicemia can be made during life only by the use of blood cultures. If, with the septicemia, we have the development of secondary abscesses, the condition then becomes a pyemia. Pyemic manifestations must, however, be distinctly separated from lesions of adjacent organs due to direct extension by continuity or contiguity. Thus we may have a streptococcus or other form of endometritis with toxemia or with septicemia; in the course of the latter pyemia may develop; or with either of the three conditions we may have local lesions due to direct extension of the infection. These terms include all possible forms of puerperal infection, but unfortunately, among surgeons and obstetricians the terms toxemia and septicemia do not receive their exact values.

Another stumbling block is the term sapremia, so frequently used for toxemia. Toxemia is now usually regarded as an intox-

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ication resulting from the absorption of bacterial products. It is possible that an intoxication may be caused by substances elaborated in the bacteria-free destruction of tissue, but there is little positive evidence to this effect. By sapremia, obstetricians usually mean constitutional disturbances, as rise of temperature, pulse, etc., accompanying the retention of the products of conception. These symptoms are supposed to be due to the decomposition of the dead tissues by saprophytes with the production of the so-called "putrid endometritis." As the bacteriology of the puerperium has been more carefully studied, these cases of putrid endometritis are found to have as a basis, infection with those forms of pathogenic bacteria more difficult of isolation. This is shown by the recent investigation of Little,[1] who found *Bacillus aerogenes capsulatus* to be not infrequently present in the uterus; and also by the recent studies of gonococcus infection by Stone and myself at the New York Lying-in Hospital. It was found that the presence of the gonococcus explained a number of cases of toxemia with constitutional symptoms which would ordinarily have been classed as sapremia. It would seem advisable, therefore, to drop the old term sapremia and group these cases as toxemia from bacterial infection.

The cases* here collected illustrate some of the more unusual forms of puerperal infection both as regards the variety of causative organisms as well as the pathologic lesions.

CASE I.—*Streptococcic endometritis with septicemia; B. aerogenes capsulatus infection; acute yellow atrophy of the liver.* Records of New York Lying-in Hospital; Case No. 7,099; primipara; aged 25; pregnancy of seven months' duration.

History.—Vomiting of pregnancy was moderately severe at fourth month; but improved towards the sixth. Two days before admission the patient induced labor by passing a button hook into the uterus, rupturing the membranes. Labor pains began shortly after and the child was partially expelled on the evening of the second day. On entering the hospital the os was dilated and the child delivered. The uterus was irrigated and packed with iodoform gauze. Vomiting was incessant at entrance, and there was slight jaundice. The temperature on admission was 102°; pulse 140. On the following day the gauze was removed. Patient was restless and noisy, but rational; vomiting severe; no abdominal tenderness. Third day, slight stupor; vomiting and jaundice increased. Fourth day, profound coma; vomiting severe; vomitus stained with blood.

*I am indebted to Drs. Lipes, Lochner and Happel for the clinical histories of the cases from the Bender Laboratory and Drs. Painter and Stone, late attending physicians to the New York Lying-in Hospital, for permission to report two cases which occurred during my service under them.

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Fifth day, comatose condition continued; incessant vomiting; conjunctivas deeply bile stained and hemorrhagic. Patient died.

Urine.—Analysis showed high specific gravity, a trace of albumin, a few blood cells, granular and hyaline casts and leucin and tyrosin.

Blood cultures were negative. Blood counts showed 3,950,000 red cells, 75 per cent. hemoglobin and 18,000 to 19,500 leukocytes. The latter were divided into small lymphocytes, 75 per cent.; large lymphocytes, 65 per cent.; polymorphonuclears, 86 per cent.

*Autopsy** by Dr. Martha Wollstein. The autopsy was performed six hours after death.

Body is that of a medium-sized woman, fairly well nourished; subcutaneous fat small in amount. There is slightly marked general icterus and a group of small subcutaneous hemorrhagic spots just below and to the left of the umbilicus.

Liver.—Not decreased in size. In the mamillary line it extended to the free border of the ribs. Weight is 1,900 grams. The liver as a whole was light yellow in color and firm in consistency. On the inferior surface of the right lobe there were areas which were softer than the rest of the liver substance, and a brighter yellowish green in color. The lobules were indistinct everywhere, the central veins being plainly visible, apparently distended, but the lobules around them are not clearly outlined. In the softer areas the lobulation is almost entirely lost. Glisson's capsule is smooth and glistening, with many small hemorrhages in and beneath it. The connective tissue septums are apparently not thickened. The branches of the portal veins are, for the most part, empty. Gall-bladder contains green fluid bile; the ducts are patent. The blood in the portal veins foams, but there are no holes in the liver substance.

Spleen.—Weighs 200 grams. Crackles on pressure. Dark red in color, soft, almost diffluent, and riddled with small holes.

Stomach—Contents dark brown and fluidless. The mucous membrane is covered with blood-stained mucus and shows punctate hemorrhages, most numerous on the posterior surface.

Kidneys.—Normal in size; capsules free; cortex not thickened; markings blurred. In the boundary zone are many small hemorrhagic areas, contrasting sharply with the gray cortex and medulla.

Bladder.—Punctate hemorrhages of the mucosa near the trigone.

Uterus.—Sixteen cm. in length. Muscle is flabby and emphysematous, and peritoneal surface is normal. The endometrium is greenish black in color and gangrenous from the fundus to the lower border of the cervical lips. Attached to the mucosa at the fundus, to the left of the median line, is a mass of placental tissue which is gangrenous.

Anaerobic cultures were made from the liver, spleen and uterine wall. *Bacillus aerogenes capsulatus* grew from each of these organs.

Aerobic cultures from the liver and endometrium, gave growths of streptococci.

Diagnosis of acute yellow atrophy of liver was confirmed by histologic examination.

*Only those portions of the autopsy protocols pertinent to the subject under discussion are given.

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Pathologic Diagnosis.—Puerperal uterus; gangrenous and emphysematous endometritis; general infection with *Streptococcus pyogenes;* acute yellow atrophy of the liver; pulmonary edema; chronic pleurisy.

CASE II.—*Double pyonephrosis; pyoureter; Staphylococcus pyogenes aureus septicemia.*

Bender Laboratory Records, autopsy 0-247.

Clinical history.—Primipara. Patient was sent to the Albany Hospital for irrepressible vomiting when 8½ months pregnant. She was much emaciated and weak. Temperature was 101°-102° at night and usually subnormal in the morning. The vomiting which had persisted for two weeks was controlled by purgatives, dieting and saline enemas; but the fever persisted. The urine showed a few pus cells but no albumin. Patient was delivered at term of a dead child. Temperature went higher after delivery and the patient died on the same day.

Autopsy by Dr. George Blumer.

Left kidney.—Measures 11x5.5x4 cm. The capsule strips readily. The surface of the kidney is pale and is dotted with purulent foci which extend into the kidney substance. On section kidney tissue is exceedingly pale. Occupying the pyramid in several cases are small abscess cavities from 2 to 12 mm. in diameter. These abscess cavities are surrounded by a distinct hemorrhagic zone. In some of the pyramids near the base can be seen minute pin-point opaque areas extending into the tubules. The pelvis of the kidney contains a small quantity of purulent material and the surface is somewhat hemorrhagic. The glomeruli are visible and the cortex measures 8 mm. in thickness. In numerous areas the infection can be seen extending up along the tubules. There is marked cloudy swelling. Left ureter slightly dilated.

Right kidney.—Measures 11x6x4 cm. Capsule strips readily; surface is pale and is studded with numerous small abscesses. There is one retention cyst, 1 cm. in diameter, on the surface. On section, the tissue of the kidney is very pale and is thickly studded with small abscesses which appear to extend up along the tubules and in places show large areas of necrosis. As in the other kidney, the abscesses are surrounded by a hemorrhagic area. The cortex measures 6 mm. The pelvis of the kidney is much dilated, contains a small quantity of purulent material and its mucosa is markedly hemorrhagic.

Bladder.—Contains about 60 cc. of turbid straw colored urine; beyond some congestion, its mucous membrane is of normal appearance. The right ureter just where it passes over the pelvic brim becomes markedly dilated and at a point near the kidney measures 2.75 cm. in diameter. Throughout the dilated portion the mucous membrane is dotted with hemorrhages and in some places clots have formed. On the left side, 12 cm. above the ureteral orifice, the ureter is dilated and measures .75 cm. in diameter, while near the kidney it measures 1.75 cm. in diameter. The mucous membrane is hemorrhagic in places. Both ureters in the region of their entrance into the bladder are of normal appearance.

Uterus.—Measures 16.5x11x8 cm. There are lateral lacerations of the cervix most marked upon the right side. The fundus of the uterus contains a considerable amount of clotted blood. The interior is much

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roughened and the surface is exceedingly irregular. Uterine muscle is of normal appearance. The vagina is much dilated and the mucous membrane shows numerous small hemorrhages. Ovaries and tubes are normal. Placenta is normal.

Microscopic Examination.—Kidneys: The greater portion of the substance shows marked cloudy swelling. Scattered here and there through the organ, usually along the group of tubules, are areas in which the kidney substance is densely infiltrated with cells, both polynuclear and small round cells. Some of these cells are in the lumen of the tubules, others are between the tubules. Associated with these lesions is a certain amount of hemorrhage between the tubules and a considerable degree of necrosis of the kidney cells. In some places there has been an extensive breaking down of the kidney substance with the formation of abscesses. The vessels are in places plugged with bacteria.

Bacteriologic Examination.—Cultures were taken from heart's blood, liver, spleen, both kidneys, pericardium and a mesenteric gland.

Cultures from the mesenteric gland and pericardium were sterile.

Cultures from heart's blood, liver, spleen and both kidneys contained in pure culture the *Staphylococcus pyogenes aureus.*

Pathologic Diagnosis.—Infection of both kidneys with cloudy swelling. Dilation of both ureters with pyoureter. Slight pyonephrosis. Acute splenic tumor. Cloudy swelling of liver. Swelling of mesenteric glands. Slight arteriosclerosis. Persistent Meckel's diverticulum. Enlarged uterus just after labor. Infection of kidneys by *Staphylococcus pyogenes aureus,* associated with general infection of blood and organs with the same organism.

CASE III.—*Periuterine thrombophlebitis; cerebral thrombosis with purulent meningitis; pulmonary embolism; streptococcus infection; pyemia.*

Bender Laboratory Records, autopsy No. 0-554.

Clinical history.—Patient had an uneventful pregnancy until the seventh month. She then suffered from angina, which was relieved in two days by treatment with gargles and silver nitrate applications. She still suffered, however, from headache, photophobia, and restlessness; evening temperature elevated from one to two degrees.

Two weeks later, when, seven and a half months pregnant, premature labor occurred without intervention. At the termination of labor immediately after the placenta had been expelled spontaneously the patient suddenly complained of breathlessness, became cyanotic, and dyspenic, and died in less than two minutes.

Autopsy by Dr. George Blumer.

Heart.—Right side contains fluid blood and postmortem clots. Endocardium and valves are normal and the average thickness of muscle of right ventricle is 4 mm. Left side contains postmortem clots; endocardium, valves and coronary arteries are normal. Auricular appendages are empty and foramen ovale is patent but is protected by a semilunar flap. Heart muscle is pale and opaque.

Left lung.—Firmly bound down by old adhesions. It is crepitant and on section slightly edematous and congested throughout. Two of the

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larger pulmonary veins contain antemorten thrombi. Bronchi show slight congestion of the mucosa.

Right lung.—Slightly adherent at the apex. It is crepitant and on section the upper and middle lobes are slightly congested and edematous. The lower lobe is markedly so. Vessels in this lung appear free from clots. Bronchial glands are slightly enlarged and pigmented.

Left kidney.—Capsule strips readily, leaving a smooth surface. On section the cortex is markedly swollen and pale, the markings are indistinct and glomeruli are scarcely visible. Veins contain fresh thrombi and a fresh thrombus is present in the main branch of the renal vein.

Uterus.—Measures 14x10x5.5 cm. The musculature is flabby, averaging 1.5 cm. in thickness and endometrium is rough; a mass of adherent material with the appearance of blood clot, is in the fundus over an area 5 cm. in diameter. The peritoneal surface is smooth. The tubes and ovaries are normal. Vaginal tissue about the cervix is cyanotic and shows a few hemorrhages. Veins in the broad ligament contain red and mixed thrombi, which are more numerous on the left side.

Brain.—Shows, on the surface, three distinct areas of softening. The largest is on the right side at the vertex in the region of the first frontal convolution, the second is on the right side in the region of the upper part of the parietal lobule and the third is on the left side, just anterior to the fissure of Rolando, involving the ascending frontal convolution.

In connection with all these areas beneath the pia-arachnoid there are collections of yellowish green pus. The longitudinal sinus contains parietal antemortem clots; the lateral sinus is free from clots.

Bacteriologic Examination.— Coverslips from the uterus show cocci in chains, not decolorizing by Gram, and bacilli decolorizing by Gram.

Cultures from spleen, bile, and meninges were sterile. Cultures from uterus and left renal thrombus show *Streptococcus pyogenes* and *Proteus vulgaris.*

Pathologic Diagnosis.—Thrombosis of veins of left broad ligament and left renal veins. Thrombosis of branches of the right pulmonary veins. Thrombosis of the longitudinal sinus. Multiple thromboses of cerebral vessels with areas of softening. Purulent meningitis over these areas. Chronic adhesive pleurisy on left side. Cloudy swelling of heart muscle, liver, and kidney. Acute splenic tumor. Puerperal uterus.

CASE IV.—*Suppurative salpingitis and perisalpingitis; lymphangitis; septic endometritis; general suppurative peritonitis from infection with the streptococcus, the gonococcus and the colon bacillus; septicemia.*

Record of New York Lying-In Hospital, Case No. 8410.

Clinical history.—Primipara, aged 18.

Previous history.—Six days before entering the hospital labor pains set in and the patient was delivered of a seven months' child by an outside physician. The child lived one hour. Bowels moved with an enema on the second day and at this time there was "fever" and abdominal pain. On the sixth day she was sent to the hospital, having suffered with pain in the lower abdomen and "fever" during this time.

Condition at entrance on sixth day postpartum.—Pulse 110, high tension, regular. Temperature 104°, no abdominal tenderness. No rigidity.

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Uterus seems well involuted. Vaginal examination shows many condylomas and profuse purulent discharge. The uterus is anteverted, soft, tender and fixed. Os admits one finger, no placental masses are felt. On palpation in the lateral fornixes, extreme tenderness is elicited. Left appendage seems negative; but on the right there is a moderate sized fixed mass. No mass or swelling is found in the cul-de-sac. Rectal examination corroborates vaginal.

Smear taken from inside of the cervix shows gonococci and streptococci. Culture from the uterus showed streptococci in pure culture. Blood culture on the sixth day was negative. Leukocyte count was 29,000, of which 90.5 per cent, were polymorphonuclears. Urine showed a trace of albumin with hyaline casts. Leucin and tyrosin were absent. The diagnosis at this time was septic endometritis with gonorrheal salpingitis.

On the seventh and eighth days her condition was unchanged. Bowels moved freely. Evening temperature was 102° with morning remission. There was slight pain in the hypogastrium. On the eighth day temperature was 103° in the evening and pulse 100. No abdominal rigidity was shown.

On the ninth day, after a large bowel movement patient complained of sudden and severe abdominal pain and difficulty in breathing. Pain was referred to the epigastrium and right lumbar region. It was peristaltic in character, intermittent, and intense. The tongue was dry and there was slight vomiting of clear green fluid. Pulse rose to 120, was thready and of high tension. Abdomen was very markedly rigid and tender. Expression was anxious and patient cried out with pain.

Vaginal examination showed slight fullness in the cul-de-sac with marked tenderness, otherwise as before. Leukocytosis at this time was 11,000, of which 89.2 per cent were polymorphonuclears.

Patient was put on the operating table four and a half hours after onset of acute pain and rigidity. Laparotomy was done under ether anesthesia in Trendelenberg position with median incision.

On opening the peritoneum large quantities of seropurulent fluid escaped. Severe general peritonitis was present with marked congestion of the visceral blood-vessels. Peritonitis was most intense in the pelvic region. Appendix was adherent to right tube and ovary. Right tube was large, much thickened and inflamed and covered with tags of adhesions. Pus exuded from the fimbriated end. There were the remains of many recent adhesions in the region of the right tube and in the right side of the pelvis. Right tube and ovary were removed with the uterus, leaving the left tube and ovary and stump of cervix. The entire peritoneal cavity was flushed with hot saline solution. Iodoform gauze drain was passed through the cervix and abdomen closed by through-and-through silkwormgut sutures, as patient's condition was poor. Death occurred after four hours without rally.

Blood taken from vein just before operation and placed on serum agar and ascitic agar yielded no growth.

Cultures taken at operation from the peritoneal pus, and from the fimbriated end of the tube showed *B. coli* and streptococci; from the inner end of the tube, no growth; from the uterine cavity, no growth.

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CASE V.—*Acute suppurative (postabortive) endometritis salpingitis; acute fibrino-purulent peritonitis; general infection with pneumococcus; pyemia.*

Records of the Bender Laboratory, autopsy 0-756.

Clinical history.—Patient, aged 20. Para II, four months pregnant. Abortion was induced by a midwife by means of a catheter. Infection resulted. She was admitted to the Albany Hospital and the uterus was curetted and packed; but she died three days afterwards. Temperature was 102° at admission and ran from 102° to 103° until death from peritonitis.

Autopsy by Dr. Stanton.

Abdominal cavity.—All peritoneal surfaces are covered with a sticky, grayish yellow, purulent exudate which is thin between adherent surfaces of peritoneum, but reaches 1 mm. to 4 mm. in thickness over the peritoneal surfaces held apart by collections of fluid. Omentum completely covers intestines, its free border reaching down into the pelvis, where it is covered with a thick layer of fibrinopurulent exudate. The pelvis and dependent portions of the abdomen are filled with a yellowish turbid fibrinopurulent exudate. The subperitoneal bloodvessels are everywhere deeply injected. The urinary bladder is distended, reaching 3 cm. above the pubes. Appendix measures 8.5 cm. in length, has a free mesoappendix, extends downward and inward over the brim of the pelvis and is negative, except for exudate on the peritoneal surface.

Uterus and appendages: These are covered with a black layer of fibrinopurulent exudate. The fimbriated extremity of the left tube is turned upward, is deeply congested and exudes a thick creamy pus when the tube is compressed. Right tube extends downward, backward and outward, the fimbriated extremity lying behind and below the ovary, and is embedded in a thick layer of the fibrinopurulent exudate. Both tubes are deeply congested, somewhat swollen and on pressure a thick cream colored pus can be forced from both abdominal and uterine ends. Mucosa of the tubes is deep red in color and is covered with cream colored pus; ovaries are deeply injected and covered with a fibrinopurulent exudate.

Uterus: This is enlarged, globular in shape, extending upward to the level of the promontory of the sacrum, is distinctly retroflexed. Cervix measures 2.5 cm. in diameter and projects 1 cm. into the vagina. Cervical canal is dilated, easily admits one finger and measures 3 cm. in length; external os is deeply congested and covered with a yellow purulent material. Uterine cavity above the internal os measures 7.5 cm. in length; the muscle is firm; the inner surface of the uterus presents a grayish granular surface with areas of bluish black and deep red discoloration. There is no evidence of endometrium.

Vagina: Negative except for congestion and bluish discoloration in the region of the cervix. This is especially marked in the posterior fornix.

Right common iliac vein contains several grayish granular masses 3 mm. to 5 mm. in diameter, the remains of softened thrombus.

Bacteriologic Examination.—Smears from the peritoneum show numer-

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ous cocci in pairs and short chains with numerous bacilli of varying morphology.

Cultures from peritoneum, liver, spleen and kidney show numerous minute translucent slightly raised colonies on agar from which are obtained lanceolate diplococci staining by Gram's method. Subcultures from these minute colonies were sterile after 48 hours. On original cultures were also moist, semitranslucent colonies 1 mm. to 3 mm. in diameter, from subcultures of which was obtained a gas-producing bacillus which coagulated milk with acid reaction.

Cultures from the uterus showed a large number of organisms which were not worked out.

Microscopic Description.—Uterus: Mucosa has been removed. Muscular walls show narrow zones of necrosis adjacent to uterine cavity. Small bloodvessels near cavity are thrombosed. Considerable leukocytic infiltration of all tissues with scattered masses of bacteria.

Tube is markedly congested and lumen is filled with pus. Serous surface is covered with an exudate of fibrin and leukocytes. All coats are infiltrated with polynuclear leukocytes and lymphocytes. Fibroblasts with a few new formed bloodvessels are found beneath the exudate on the peritoneal surface. Gram-Weigert stains show numerous cocci in pairs and short chains, and long rod-shaped bacilli.

Pathologic Diagnosis.—Acute suppurative salpingitis and endometritis. Acute fibrinopurulent peritonitis. Mural thrombus of right heart. Congestion and edema of the lung with hemorrhages. Slight cloudy swelling of liver and kidneys.

CASE VI.—*Acute hemorrhagic endometritis; acute suppurative peritonitis and pericarditis; septic pneumonia with pleuritis; Staphylococcus pyogenes aureus infection; pyemia.*

Bender Laboratory Records, autopsy 0-198.

Clinical history: After an apparently normal pregnancy, patient was delivered by a midwife and entered the hospital on the eighth day postpartum very profoundly infected. Death occurred 36 hours after, her condition being so bad that nothing could be attempted in the way of operative measures.

Autopsy by Dr. George Blumer.

Peritoneal cavity contains about 300 cc. of turbid purulent fluid. Both layers are dull, injected and covered with a small amount of fibrin. Intestinal coils and omentum are adherent to one another by fresh adhesions. Appendix is normal. Retrosternal glands are not enlarged.

Pericardial cavity: Distended with 250 cc. of turbid yellow fluid. Both layers are dull and slightly injected.

Left pleural cavity: Contains about 1,000 cc. of turbid serous fluid. Right pleural cavity also contains turbid fluid.

Left lung: Pleura is covered by layers of fibrin and lymph. Both lobes are crepitant and on section are congested and edematous. Bronchi are congested and covered with mucopurulent fluid. Bloodvessels are normal.

Right lung: Bound down by fresh adhesions on all its surfaces. Pleura is also covered by layers of fibrin and lymph. Lung is less

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crepitant than normal and lower lobe feels quite solid. On section lower lobe shows bronchopneumonic areas and elsewhere lung is congested and edematous.

Uterus is enlarged, subinvoluted, soft and measures 12 x 8 x 5 cm. Peritoneal covering is injected and covered with a plastic fibrinous exudate. The os is patulous and escaping from it is a large amount of sticky blood-stained material. The endometrium is markedly congested and shows a few discrete submucous hemorrhages, the mucosa is covered with tenacious foul mucoid fluid. Uterine walls are 2 cm. in thickness. Mucous membrane of the vagina is congested and shows a few hemorrhagic points. Tubes and ovaries are apparently normal.

Bacteriologic Examination.—Smears from fluid of pleura, pericardium and peritoneum contain many polymorphonuclear leukocytes with round cocci, generally single, which do not decolorize by Gram's method.

Cultures from spleen and gallbladder are negative. *Staphylococcus pyogenes aureus* is obtained in pure culture from liver, pleura and uterine cavity. Cultures from the bronchopneumonic areas of lung and from peritoneum show colon bacillus as well as *Staphylococcus pyogenes aureus.* Kidneys give a pure culture of colon bacillus.

Pathologic Diagnosis.—General infection with *Staphylococcus pyogenes aureus.* Infection of kidney, lung and peritoneum with *B. coli communis.* Bronchopneumonia with edema of the lungs. Acute bronchitis. Fibrinopurulent peritonitis, pericarditis and pleurisy. Acute splenic tumor. Cloudy swelling of kidney. Subinvoluted uterus with acute hemorrhagic endometritis.

Discussion of Cases.

Case I.—Legg's statistics show that 69 of 100 cases of acute yellow atrophy occurred in females and in 25 there was the association of pregnancy. Thierfelder collected 143 cases, of which 88 occurred in females and in 33 instances it was associated with pregnancy. However, acute yellow atrophy is also found in association with many other conditions and with bacterial infections. Among the bacterial diseases may be mentioned typhoid fever, diphtheria, erysipelas, osteomyelitis and puerperal infection. Richter[2] has collected 41 cases of acute yellow atrophy in association with syphilis. Babes[3] has reported 5 cases following streptococcus infection and Ballin[4] has collected 10 cases following chloroform anesthesia.

Hyperemesis gravidarum is a not infrequent association with acute yellow atrophy. Stone[5] reports one case of acute yellow atrophy with this association and collects a large number of others. Meyer-Wirz[6] among other degenerative changes in the liver of patients dying from eclampsia found one case of acute yellow atrophy, not associated with puerperal infection.

The frequent occurrence of infection in association with

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eclamptic and other toxemias of pregnancy is well known. Schrieber[7] in a statistical study, reports that out of 29 deaths with eclampsia 7 died of sepsis, and Meyer-Wirz,[8] in 117 cases of eclampsia, had 35 deaths, in which puerperal infection had supervened in three and in an additional case there was septic pneumonia. However, the toxic symptoms, as shown by the vomiting, were not severe in the case reported here; but it seems that the association of infection and pregnancy is a factor of some significance in the production of acute yellow atrophy of the liver. Strictly speaking, this should, perhaps, be considered a complication of pregnancy rather than an example of puerperal infection. In view, however, of the probability of the infection beginning in the genitalia it may justly be considered here.

CASE II.—Pyonephrosis is a rather uncommon complication of pregnancy, but hydronephrosis and dilation of the ureters does not appear to be so. Olshausen[9] has reported 16 cases of dilation of the ureter, in 12 of which the condition was unilateral and in 10 of these on the right side. This distribution is supposed to be due to the greater frequency with which the fetal head lies in the right oblique diameter of the pelvis. In this case the position was l. o. a., but the measurements of the pelvis were not noted. It may be possible that a generally contracted pelvis with an obliterated promontory would permit pressure to come upon both ureters at the pelvic brim and cause such dilation of the ureters as occurred in this case.

Cragin[10] in a study of 10 cases of pyelitis complicating pregnancy, states that according to Vinay[11] this condition depends upon two etiologic factors: (1) Pressure of the ureter by the pregnant uterus; (2) infection of the urinary tract above the point of compression. Cragin states that in his cases the clinical course was marked by right-sided pain, sometimes elicited only by palpation or sudden motion. A rise of temperature usually occurred. He states that irritability of the bladder with frequent micturition is common, but that "the infection is a descending one and cystitis, when it does occur, is usually secondary to the pyelitis and ureteritis."

The experiments of Rebdaud and Bonneau upon animals are quoted in support of this view. These investigators produced pyonephrosis by aseptic ligation of the ureter and the injection into a distant part of the body of streptococci or colon bacilli.

The case reported, because of the exemption of the bladder

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and the lower part of the ureter, seems to have been a descending infection. Staphylococcus infection in such cases is rare; colon infection is by far the most frequent cause according to the collected cases of Cragin. One instance of streptococcus infection has been reported by Vinay and one of gonococcus by Loy.

It is interesting to note in view of the recently advanced theory of the common origin of eclamptic toxemia and toxemia of pregnancy with vomiting that this case was admitted to the hospital for pernicious vomiting and that Meyer-Wirz in his 35 autopsies for eclampsia noted bilateral hydronephrosis and dilation of the ureters in one case.

Rochard[12] reports a case of severe bilateral pyelonephritis in advanced pregnancy with immediate recovery after delivery of twins. He quotes Kendirdjy's statistics of 62 cases among which there were only two deaths, and advises expectant medical treatment, but states that if interference is necessary premature delivery should be the rule rather than an operation on the kidney. Cova[13] has reported 21 cases in which nephrectomy was done with resulting abortion in only five. The danger of involvement of the second kidney is so great that it would seem preferable to remove the cause of compression of the ureter rather than to remove the kidney.

Fournier[14] has reported two cases of this condition with varied course. In one there was gradual onset in the early months of pregnancy, premature labor and birth of a dead child at seven months. In the other there was an acute attack, nephrotomy and labor at term. Schwab[15] also reports two cases, in one there was a history of gonorrhea and the infection was severe, but patient went to term. The second case was one of hydramnios and ran an apyretic course. The colon bacillus was the infecting organism and a live child was born at 8 months of pregnancy. Schwab draws attention to the difficulty of diagnosis and of the difficulty of differentiating from appendicitis.

Cathala[16] in a clinical and pathologic study of pyelonephritis in pregnancy states that there are two main causes: (1) Predisposing cause, the lessened resistance of the pregnant woman to bacterial infection and the retention of urine from compression with its associated congestion. (2) Determining cause, the penetration of the infecting organism to the kidney. He divides the clinical course into two periods: that of onset, in which there are symptoms of general infection; and that of attack, in which

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there are symptoms of chronic suppurative pyelonephritis. He concludes that the prognosis for the child is bad, for if pregnancy does go to term, the infant not infrequently is of small size and weak.

CASE III.—Periuterine thrombophlebitis is a most serious condition and is the most frequent predisposing cause of pulmonary embolism and sudden death in pregnancy. Grossman in a study of 51 autopsies upon puerperal women dying from infection found periuterine thrombophlebitis alone in 14 instances and associated with lymphangitis in 13 other instances. Other veins in addition to the hypogastric and ovarian were involved in all cases save one; in three instances the vena cava was also included.

Richter[17] lays stress upon Mahler's sign ("Kletter symptom"), the rapid beat of the heart due to extra work and slight degeneration. He has collected results from 16,000 cases and found 78 cases of thrombosis and 20 cases of embolism; of the last 60 per cent were fatal. Mahler's sign was found in 98 per cent of these cases.

The thrombosis may be due to mechanical causes, but is more frequently associated with infection. The initial lesion in the case reported here would appear to be the infectious process in the throat. This case is possibly, therefore, one of autoinfection, as is the case of pyonephrosis.

CASE IV.—Gonorrheal infection in the puerperium has been much discussed among obstetricians and widely divergent opinions are held in regard to its incidence and its influence upon tissues altered by pregnancy.

Kronig's[18] study of 179 cases of puerperal fever showed that *M. gonorrhoeae* was found in 50 cases, while Williams[19] found the organism in 8 of 150 cases of puerperal fever. Vogel[20] in 24 cases of puerperal fever found gonococci 4 times, twice in pure culture and twice in association with streptococci. Foulerton and Bonney[21] examined 54 cases with negative results. Stone[22] and myself, in a study of 53 selected cases of pregnancy, found the gonococcus in 17. In three cases labor was premature.

Martin[23] kept under observation 13 cases of chronic gonorrhea during labor and the puerperium and in none of these were symptoms observed which could be attributed directly to the venereal disease. There were no abortions, although in one case labor was hastened by an acute exacerbation of the disease. In four cases the puerperium was practically normal and in the re-

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mainder there was a rise of temperature coming on rather late. This the author considers characteristic of the disease.

Lea,[24] taking acute purulent conjunctivitis in the infant as a proof of gonorrheal infection of the mother, has collected 50 cases. In 60 per cent there was an uneventful puerperium, while 40 per cent. had more or less acute inflammation of the pelvic organs. Acute purulent endometritis with pyrexia as the most common condition, while in 10 per cent acute pelvic peritonitis existed. All the patients recovered save 3, who were also infected with the streptococcus. In institutions, however, acute purulent conjunctivitis in the child is not a just criterion of the frequency of gonorrheal infection of the mother, for Holt[25] has noted the frequent transmission of gonococcus infection among infants that are segregated in hospitals.

The presence of a mixed infection of the gonococcus and some other organism is said to add greatly to the severity of the infection and many cases have been reported to sustain this view. However, the severity of the constitutional symptoms seems to depend more upon the extent of the anatomic lesion than upon the character of the infection.

CASE V.—Pneumococcic puerperal infection is an extremely rare condition and is usually an infection from without. Weichselbaum,[26] as well as Bar and Tissier,[27] have met this condition, and Cohn has described a case very similar to the one here reported. His patient after abortion developed a pneumococcic endometritis and later a fatal meningitis. Foulerton and Bonney[21] also report a similar postabortive infection from pneumococcus with five other cases of pneumococcus infection following full term pregnancies. They conclude that the grade of infection is, as a rule, not severe and that their series of cases cannot be taken as a just indication of the frequency of this form of infection.

CASE VI.—General septicemia is not an infrequent termination of puerperal infection. The clinical course is usually that of a rapidly progressive acute infection and follows the same course as other septicemias not of puerperal origin. Streptococcus infection is the most frequent and severe type of infection after labor. If the number of cases studied by Czerniewski, Kronig, Williams, Vogel and Foulerton and Bonney be collected, it is found that of 498 cases in which the contents of the uterus was examined bacteriologically, streptococci were present in 200 (40 per cent). While streptococcus is so frequent, *Staphylococcus pyogenes*

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aureus is most infrequent. Foulerton and Bonney found this organism but once in 54 cases and it is but infrequently mentioned by other writers. *Staphylococcus pyogenes aureus* was found in two of the six cases in this study; in one the infection was of the kidney and in the other an acute general infection of all the organs.

Conclusions.

A consideration of these six cases teaches many things in regard to the diagnosis and management of puerperal infection in the more advanced stages of the disease. It may be seen that while streptococcus infection is usually the most common and severe type of infection, other organisms which usually produce clinically mild symptoms, may run a severe course and cause death.

Autoinfection must be considered to include infection from foci of bacterial disease in distinct parts of the body. Pregnant women suffering from such distant infection require most watchful care. Autoinfection from the genital canal is probably more common than is generally supposed. This is indicated in a study by Bumm and Sigwart[28] of the bacteriology of the secretions of women in the later months of pregnancy. The streptococcus was found to be present in more than 38 per cent. of the cases and they conclude that with very careful examination aerobic streptococci may be found in the secretions of at least 75 per cent of all women during pregnancy and the puerperium. Of the women having streptococci, 20.4 per cent had fever.

From this fact it may be seen that the presence of pathogenic microorganisms in the genital canal is by no means sufficient evidence upon which to base a diagnosis of puerperal infection, and even when combined with constitutional disturbances the first step only has been taken toward the proper diagnosis of the condition. The term puerperal infection should be broadened to include infection elsewhere than in the uterus, and the location and nature of such lesions should be recognized before any operative measures are undertaken. This can only be done by exact physical examination, examination of urine, blood, etc., and a proper knowledge of the varied anatomic manifestations of infection. The frequency with which pain is right-sided in hydronephrosis and pyelitis should be remembered in differentiating the diagnosis from appendicitis.

The utter futility, and even harmfulness, of curettement, if at-

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tempted in such cases as those here reported, is readily seen; and when the varied character and oftentimes widespread distribution of puerperal infection are considered, the explanation for the high mortality (over 70 per cent) of hysterectomy in that condition is obvious.

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A NOTE ON EMBRYONIC GLANDULAR TUMORS OF THE KIDNEY WITH THE REPORT OF A CASE.

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(From the Bender Laboratory, Albany, N. Y.)

In 1899 Birsch-Hirschfeld, in a study of the tumors of the kidney, classified as embryonic glandular tumors those new growths which formerly had been termed adenomyoma, adenosarcoma and adenomyosarcoma, names which were descriptive of the tissues of the tumor but which did not indicate their origin. He proved that these tumors had a common origin in embryonic life.

Such tumors are not of infrequent occurrence, forming as they

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do twenty-eight per cent. in Walker's collection. They occur nearly always in children; only two cases have been reported in adults, that of Hoisholt in a male of eighteen years and that of Muus in a female of thirty-four years. Their growth is rapid and they metastasize early and after removal generally recur *in situ*. In spite of their malignant nature this form of tumor has attracted very little attention in this country, for from 1899 until the present time I have found only one reported case, that of Blumer in 1903.

All these tumors have in common a glandular tissue and an embryonic or archiblastic tissue which resembles closely that of sarcoma. In addition to these tissues smooth and striated muscle, cartilage, fat and connective tissue are commonly present. They grow almost without exception in the pelvis or medulla of the kidney and extend outward toward the cortex, gradually compressing the kidney tissue until it forms a capsule for the tumor. Metastases develop generally by way of the blood vessels and but rarely by way of the lymphatics. The various tissues of the primary growth are reproduced. The minute structure of these tumors varies within wide limits, owing to the variable proportion of the tissues present.

The case here reported occurred in the practice of Dr. Charles S. Jennings of Detroit, Mich.; no clinical notes or autopsy report could be obtained.

The exact dimensions of the kidney cannot be determined because the specimen has been sectioned and portions removed. The tumor is nearly globular, located within the substance of the kidney and measures 3.5 cm. in diameter. The surface is fairly smooth with here and there furrows marking definite lobulations; the consistence is firm. It is partially surrounded by kidney substance which forms a capsule 0.6 cm. in thickness and where the kidney tissue ends the fibrous capsule continues over the tumor.

On section the tumor is solid and of fibrous structure. Definite masses of fibres arranged in large bundles pass in various directions and give to the tumor an appearance identical with that of a myoma of the uterus.

Attached to the kidney at the hilum is a considerable amount of fibrous tissue in thin layers suggesting that it may have formed the wall of a large cyst the contents of which have been lost. In this tissue are some smaller cysts containing a colloid-like material and numerous large blood sinues. The exact relationship

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of the cysts to the kidney cannot be made out because the specimen has been so badly torn.

The microscopic appearance of the parenchyma of the kidney is normal; there is, however, on the outer surface of the capsule an exudate of fibrin and polymorphonuclear leucocytes indicating a perinephritic infection.

The tumor has no distinct capsule separating it from the kidney substance and in places it invades the kidney. The growth at no point extends beyond the capsule of the kidney. Its finer structure presents a much more complicated picture than the gross appearance indicates. Several varieties of tissue are to be considered, as follows:

A.—Glandular tissue in the form of tubules running in all directions, appearing in longitudinal and cross section. These tubules are apparently of two kinds—those belonging to the kidney which have been enclosed in the peripheral parts of the tumor, and those which form an integral part of the growth. This second form of tubule originates in the youngest portions of the growth from accumulations of small round deeply staining cells situated in and derived from the archiblastic tissue. The glandular elements are small in amount and form only a small part of the tumor.

B.—Embryonic or archiblastic tissue forms a considerable portion of the tumor and represents that portion which is growing most rapidly. In appearance it closely resembles sarcomatous tissue; the cells are large, round or oval, with pale staining nuclei and are packed closely together with no stroma. It is in this tissue that the groups of small round cells are found from which the tubules are developed. Blood spaces are very numerous in some parts of this tissue so that it resembles angio-sarcoma closely. At the hilum this tissue forms long cylindrical projections which rapidly undergo degenerative changes. In the more advanced of these the archiblastic tissue is replaced by what appears to be fibrous connective tissue often mucoid in character. The connective tissue at the periphery rapidly undergoes hyaline degeneration so that finally the cylinder consists of a central axis of mucoid connective tissue surrounded by a mass of homogeneous hyaline-like material. Blood vessels are very numerous in these projections, while glandular elements are relatively scarce. Several dilated, almost cystic, spaces were found in the cylinders lined by flattened epithelium which suggests that probably the

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cysts mentioned in the gross description were formed in this way from the tubules.

In the absence of any autopsy record the presence of metastases was not determined.

In reconstructing the tumor from the individual tissues that have been described we find that the smooth muscle represents the oldest portion and is located in the substance of the kidney growing into it and enclosing tubules and glomeruli. For this reason tubules and glomeruli are found in the myomatous portion of the tumor.

The archiblastic and glandular tissue represent the youngest and most rapidly growing portion of the tumor and is always found at a distance from the kidney. It extends into the fibrous tissue at the hilum in the form of cylinders as described above. The cartilage fat and connective tissues are very scanty in amount and are found near the archiblastic tissue.

From this description it is clear that this tumor began its growth within the kidney, probably near the hilum, that it is of congenital origin and that it must be classed as a mixed tumor, belonging to the group classified by Birsch-Hirschfeld as embryonic glandular tumors.

The method of development of these tumors has been the subject of much controversy and several theories have been advanced which for the convenience of description may be divided into two groups.

A.— The development of the tumor from cells within the kidney. The older view that these tumors should be classed as primary carcinomata or sarcomata of the kidney is no longer considered correct. A carcinoma develops from fully developed epithelial cells in an adult organ, whereas these tumors are found almost exclusively in very young children and metastasize by way of the blood vessels. To be classed as sarcoma it must be assumed that the glandular tissue has sprung from kidney tubules, which is not the case, as has been seen in the tumor just described. The tubules are an integral part of the tumor and take an active part in its growth.

The more recent view that these mixed tumors have their origin in tissues present in the kidney of the embryo is supported by Busse and Muus. The former found, in a fœtal kidney, tissues which closely resemble those occurring in these tumors and

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he is convinced that the tumors take their origin from such tissues.

Muus believes that a portion of the embryonic kidney takes on a pathological growth and so forms a tumor. The various tissues of the tumor are supposed to originate by metaplasia from the tissues of the embryonic kidney, thus sarcoma-like tissue from round cells, epithelium from the interstitial tissue, mucoid tissue, cartilage and fat from connective tissue, smooth muscle from that normally present in the kidney, striated muscle from smooth muscle.

B.—The theory that the tumors originate from embryonic cells outside the kidney but enclosed during development. This view is strongly supported and was originally advanced by Birsch-Hirschfeld, who believes that a portion of the Wolffian body in the embryo in some way becomes enclosed in the developing kidney and forms the starting point of the tumor. Vogler, Merkel, Heincke, Sander and Blaess also accept this view. Wilms calls attention to the fact that the Wolffian body contains no striated muscle and that none is present in any of the organs developing from it. The metastases furthermore contain all the varieties of tissue found in the main tumor, so that a metastasis of cells representing all these tissues is unlikely. He concludes from this that the origin of the tumors must be placed at a much earlier period of embryonic development when the cells are undifferentiated, that is, germinal tissue cells which in their later development are capable of forming all these various tissues.

These cells might be misplaced at the time when the primitive segment and lateral plates are formed from the middle germinal layer. The striated muscle develops from the myotom of the primitive segment from which all the striated muscles of this region develop. The smooth muscle, fat, connective tissue and cartilage originate from the scleratom of the lateral plates while the epithelium originates from the nephrotom (Wolffian body).

If a small portion of these structures become misplaced and take on a pathological growth it would readily explain the various tissues found in these tumors.

The presence of cysts in association with these tumors has not been mentioned so far as can be found in the literature. The formation of the cysts in the tumor here described seems to have taken place either by hæmorrhage and degeneration in the archiblastic tissue or in a gradual dilatation of the tubules. This view

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lends support to the theory already generally accepted that cysts of embryonic origin result from misplaced mesodermal tissue.

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TUBERCULOSIS OF AN ADENOMYOMA OF THE UTERUS.*

BY J. L. ARCHAMBAULT, M. D.

WITH A PATHOLOGIC REPORT

BY RICHARD M. PEARCE, M. D.

(*From the Bender Laboratory, Albany, N. Y.*)

That tumors in general are not subject to invasion by bacteria, other than those of the pyogenic group, is well known. The simultaneous occurrence of carcinoma and tuberculosis in an organ or tissue is occasionally reported, but the invasion of other tumors by the tubercle bacillus is very unusual. This is especially true of uterine myomata which are seldom involved in even the most extensive tuberculous infections of the adjacent mucosa. The case here reported is of interest not merely on ac-

*Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906. Published also in Jour. Amer Med. Assoc., 1906, xlvii, 768.

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count of the rarity of the condition, but also because of the absence of tuberculosis in the mucosa of the general uterine cavity with but a slight lesion in one tube. The tuberculosis of the myoma and that of the tube were secondary to tuberculosis of the lung, but apparently independent of one another and due to infection through the blood stream. As a fairly exhaustive review of the literature fails to reveal an analogous condition our observation appears to be worthy of record. A detailed report follows:

Clinical History.—H. E., aged 20, an only child, unmarried, was admitted to the Cohoes Hospital, January 10, 1906. Her family history offers several points worthy of note. Her mother presents evidence of tabes and her father died at forty-six of a valvular lesion of the heart which formed part of the plainly luetic condition. Her grandfather, on the mother's side, had syphilis, and the grandmother succumbed to general paralysis. There is no direct tuberculous heredity.

Personal History.—The patient had measles in early childhood and showed some indications of hereditary syphilis, viz.: A slowly-healing ulcer of right leg and a nose of the saddle type.

Menstruation beginning at sixteen, has always been very scanty, irregular and tardy, with occasional amenorrhea for periods of five to six months. An epistaxis, apparently vicarious, had been frequent. Menstruation, at first painless, later became more difficult. At no time had there been leucorrhea. Dec. 14, 1904, a pelvic examination showed the uterus to be very small, of the infantile type, and lying in a moderate degree of retrodeviation, with some tenderness in the region of the left ovary.

July 30, 1904, the patient had a sudden attack of hemoptysis. A careful physical examination gave evidence of a localized adhesive pleuritis of the left apex, overlying an area of tuberculosis, involving a considerable part of the apex and extending down and outward toward the axillary line. After a sojourn at the seashore and in the mountains she was considerably improved in general health, while the physical signs had manifestly retroceded and in part entirely disappeared. The following winter (1904) was passed in the mountains and she returned in April still more improved. July 15, 1905, she had a second very slight hemoptysis, but improved rapidly, gaining by November 13, twenty-nine pounds.

Present Illness.—Abruptly, about November 21, she began to complain of soreness and pain in the hypogastric region. The pain was dull in character, intermittent, returning especially in the latter part of the day, and exaggerated by fatigue and standing. The patient had not menstruated in five months. As the pain continued unabated for a week, without any appearance of the menstrual flow, she was advised to return home. On bimanual examination, the cervix was found deviated toward the pubes and the Douglas cul-de-sac occupied by the enlarged fundus of the retroverted uterus. The fundus gave the sensation of a firm mass of about the size of a mandarin and somewhat irregular in

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shape, being larger on the left, and very slightly movable. The left lateral cul-de-sac was also occupied by another swelling less firm and less voluminous, having neither the fibromatous woody feeling of the main tumor nor the fluctuation of a cyst; this second enlargement seemed almost contiguous with the uterine body. The condition of the right adnexa could not be defined. These conditions were not present at the previous examination, eleven months before.

At this stage, the pulmonary condition presented a marked change. While no advancement of the disease was evident in the left apex and the corresponding axillary region, two new foci had appeared; one in the left base posteriorly and the other in the right interscapular space, close to the spinal column.

December 15, menstruation occurred and lasted five days. After a few days interruption, there was again some slight bloody discharge. This discharge kept on thereafter, more or less irregularly, until the time of operation. The pains became gradually more intense, finally requiring the daily use of some sedative for their control.

January 5, the size of the pelvic mass was considered to have increased materially. On that same date, a few tubercle bacilli with a great number of diplococci and streptococci were found in the sputum. Three previous examinations of the sputum had been negative.

Much concern was naurally entertained as to the exact nature of the uterine condition. The first diagnosis was simply one of a solid tumor, probably a fibromyoma, occupying the posterior wall of the uterus. A closer study, however, of all the evidence suggested the possibility of a tuberculous lesion of the uterus, and this possibility was carefully explained to the family.

Of course, on account of their rare occurrence, the diagnosis of any of the pelvic forms of tuberculosis is seldom made until the abdomen is opened, and even then not infrequently only after the specimen is in the hands of the pathologist. Uterine tuberculosis has no well-defined symptomatology. In the present instance, if a probable diagnosis of a tuberculous condition of the uterine growth was arrived at before operation, it is willingly conceded that we expected to find as well a similar condition of the adnexa and of the peritoneum; that is, a general abdominal tuberculosis. In holding this view, we were influenced by the existing pulmonary condition and by abdominal symptoms which predominated especially during the very last weeks. When the abdomen was opened, it was a surprise, therefore, to find that, aside from numerous and extensive adhesions of an inflammatory nature, the general as well as the pelvic peritoneum was free from tuberculosis.

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Surgical Report.—January 11, laparotomy; medium incision nine centimeters long. A coil of small intestine was found drawn down into the pelvis and firmly adherent close to the right uterine cornu, evidently accounting for the pain in the abdomen which had been so striking a feature. Both ovaries were fibrocystic. The uterine body, enlarged to the size of an orange, lay deeply in Douglas' cul-de-sac and was so matted up in adhesions that a subtotal hysterectomy was performed. The appendix was inspected and, being healthy, was left undisturbed.

Convalescence was uneventful, and the patient reported April 16, that she had gained ten pounds in weight and was in the best of health.

PATHOLOGIC REPORT BY DR. RICHARD M. PEARCE.

Gross Description.—The specimen consists of a uterus with its appendages. The former is exceedingly firm and almost globular in shape, measuring 17.5 cm. in circumference just below the level of the attachment of the Fallopian tubes and 19.5 cm. over fundus and cervix. The cervix protrudes beyond the globular body as a short, thin, circular process, 0.8 cm. long and with walls 0.4 cm. thick. Its edges are smooth, rounded and grayish-white in color. The peritoneal surfaces are covered more or less uniformly by coarse fibrous adhesions. On section the entire length of the uterus from cervix to fundus is 6.8 cm., the greatest thickness, antero-posteriorly, 5 cm. The body itself is 6 cm. in length. The anterior wall is normal in appearance, though slightly thickened, and measures 1.4 cm. at the mid portion of the uterine cavity. The fundus is 1.7 cm. in thickness. The posterior wall is occupied by a globular mass extending from the median line of the fundus to the internal orifice of the cervix (5.2 cm.) and laterally from the peritoneum to the uterine cavity (4 cm.). This mass is composed of firm, dense, grayish-white tissue having a whorl-like appearance and resembling the structure of myoma in a general way, but riddled everywhere by cavities varying from those miliary in size to those 0.5 cm. in diameter. From these cavities escapes a thick, yellow, more or less tenacious pus. The walls of the larger cavities, after the escape of the fluid pus, are seen to be lined by a yellow, soft granular material, suggestive of caseation. These areas extend to within two millimeters of the peritoneal surface and toward the median line approach and apparently involve the mucosa. The cervix is not involved. The uterine canal is 4.7 cm. long, 1.2 cm. of which is cervical. It is greatly narrowed and 2 cm. below the fundus is almost entirely obliterated. In or beneath the mucosa covering the lower portion of the tumor are numerous closely-set, fine, yellowish miliary areas. These do not involve the mucosa of the anterior wall nor that of the cervix.

The tubes and areas are atrophied. The left tube and ovary are bound to the uterus by fibrous adhesions; the right is free and has a smooth peritoneal covering. Each ovary contains a few small cysts.

Bacteriology.—Cover glass preparations of material from the cavities in the tumor, stained by methylene blue, show pus cells which take the stain well, many poorly-staining necrotic cells, and much granular

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detritus but no micro-organisms. Attempts to demonstrate the tubercle bacillus and the gonococcus are negative.

Agar, blood serum and hydrocele-agar tubes are sterile after 72 hours.

Histologic Description.

Sections Passing Through Uterine Wall and Tumor.—The greater portion of such show a diffuse tuberculous process in a tissue composed of smooth muscle fibers and containing widely scattered tubular glands. The uterine wall proper, measured beneath the cover glass, is 3 mm. in thickness. No tubercles are present in the slightly thickened peritoneal covering, but between it and the musculature small tubercles are occasionally seen. In the muscle itself, which contains an increase of connective tissue, are a few well-developed tubercles with caseous centers. About the blood vessels are numerous lymphoid cells. The line between the normal uterine musculature and the tumor in the upper portion of the uterus is intact, but in the submucosa are irregular accumulations of lymphoid cells. At a point where the definite arrangement of the musculature ceases there is an abrupt transition to diffuse tuberculous tissue containing numerous giant cells and characterized by extensive caseation; few typical tubercles can be seen. In the midst of this are found here and there isolated areas of smooth muscle, containing tubular glands. These latter are lined for the most part by several layers of cylindrical cells, of the type found in the uterine glands, but are tortuous and show more or less irregular dilations. They are not infrequently arranged in clusters and have branching prolongations with but a single layer of epithelium. In the masses of muscle a moderate amount of connective tissue is present and also a slight infiltration of lymphoid cells. The glands are found throughout the new tissue, even at a distance of 2 cm. from the uterine wall and have no relation to those of the mucosa. There is no evidence that the channel of the tuberculosis infection was along these glands.

Sections taken at three levels and passing through entire wall of apparently normal portions of uterus opposite tumor show no evidence of tuberculosis. The mucosa in each is normal. A section through the cervix shows no lesions.

A section across the entire uterine canal at a point of greatest constriction shows partial obliteration, but no tuberculosis of the mucosa. The lumen at this point contains a small plug composed of mucus, leucocytes and desquamated epithelial cells.

Right Fallopian Tube.—The mucosa is entirely destroyed. The surface is a chronic granulation tissue with, in its deeper layers, more or less newly formed fibrous tissue. Epithelioid cells are not abundant and are very diffusely arranged. But one definite tubercle with typical giant cell is seen. An occasional oval fibrous and hyaline area is suggestive of healed tubercle, as are also a few small foci of lime salts. In the deeper layers of the muscle coat are accumulations of lymphoid cells and old blood pigment, but no tubercles.

The left Fallopian tube is atrophied, but otherwise not noteworthy. The

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ovaries are fibrous and contain a few small cysts, but show no evidence of tuberculosis.

Careful examination of the peritoneal surfaces of the uterus, tubes and ovaries fails to reveal lesions of tuberculosis.

Pathologic Diagnosis.

Tuberculosis of an adenomyoma of the uterus. Tuberculosis of right Fallopian tube. Atrophy of ovaries and Fallopian tubes. Chronic perimetritis and perisalpingitis.

Remarks.

As already stated, we have made a search, although not exhaustive, of the medical literature for analogous cases, but have failed to find such.

Closely resembling the case here reported, however, is one observed at the gynecologic clinic of Zurich by C. Bole (du Locle).[1] A summary of this case reads as follows:

History.—Woman, aged 50; heredo-tuberculosis; menstruation at thirteen; leucorrhea. Patient married twice, no children. Dysmenorrhea and loss of strength.

Present State.—Uterus anteflexed, movable, slightly tender on pressure and about the size of a child's head in volume.

Diagnosis.—Uterine myoma.

Laparotomy.—Total hysterectomy after Freund's method. The tumor, when extirpated, is twice as large as one's fist. The macroscopic and microscopic examination showed that it was a rare case of myoma associated with an ascending uterotubal tuberculosis. The vaginal mucosa was not involved, and the etiology could not be determined.

This case, however, is not identical with the one here reported. The tumor is intramural, but the tuberculosis is spoken of as an ascending uterotubal infection, and the myoma as associated with it. From this it may be inferred that the mucosa alone was involved in the tuberculous process. This inference also finds support in the statement that the histologic researches bore only on "the superficial portions, in a state of necrosis." Thus it would appear from these comparisons that our case might indeed, deserve to be considered as unique.

Kelly[2] states that "tuberculosis of the endometrium is exceedingly rare as complication in the large myomatous uterus." He has met but one case, and in this the disease had extended into both tubes.

A last point not to be overlooked is the mode of infection or of transmission to the uterine parenchyma.

[1] Gynækologia Helvetica, 1903, p. 99.
[2] "Operative Gynecology," vol. ii, p. 381.

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As regards the pathogenesis of the local lesions in our case, it seems very plausible that the adenomyoma constituted the primary lesion and that the tuberculous infection occurred secondarily. But how did this infection take place? How in this particular case was it transmitted from the lungs?

From the clinical history and from the findings at the time of the operation it seems fair to believe that the propagation of the lesions to the uterine tissue took place through the blood current, and in a similar manner, to the only tube involved.

Infection by means of the blood stream seems to be well supported by the conclusions of M. Schakoff,[8] which may be given as follows:

Genital tuberculosis in women is generally secondary to a florid or latent tuberculosis of the lungs or of the peribronchial lymph nodes, less frequently to an intestinal tuberculosis. The genital tuberculosis is generally propagated by the blood stream, except in the case of vaginal tuberculosis, which may proceed from inoculation by contact.

Tuberculous peritonitis occurs frequently during the evolution of a genital tuberculosis, especially after a tuberculous salpingitis. Any portion of the genital tract may be affected; the tube is involved more frequently, the vagina less often. These inoculations take place by the blood stream; therefrom the uterus or the ovary may become infected by contiguity. Generally the uterus is infected by descending contagion; it may, however, be involved in the first place. A pre-existing disease and the puerperal state may act as predisposing causes. The uterine cervix is rarely the seat of tuberculosis. The tuberculosis of the ovary is almost always consecutive to a tuberculosis of the Fallopian tube, of the peritoneum, or of the rectum; the propagation occurs by contiguity or by way of adhesions. Independent foci may, however, be found in the ovary without any lesions of the surrounding structures; in such cases these foci have been set up by the blood stream.

In the above conclusions, the two points of practical bearing on our case are: 1. Genital tuberculosis in women is generally secondary to pulmonary tuberculosis. 2. In tuberculosis of the uterus or of the ovary, when the tuberculous lesions are found as independent foci without lesions of the surrounding structures,

[8] "Contributions to the Knowledge of Tuberculosis of the Female Genital Organs," Gynäk. Helvet., 1904, p. 139.

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the inoculation has taken place by the blood current. That the latter would appear to be the case is indicated by the absence of tuberculosis in the mucosa, not only of the uterine cavity generally, but also in that covering the tumor itself. It is possible that alterations in the blood supply of the tumor caused a condition of degeneration or necrosis constituting a *locus minoris resistentiæ* and a point of selection for tubercle bacilli reaching these areas through the blood stream.

A REPORT OF FOUR INSTANCES IN WHICH GIANT CELLS OCCURRED IN UNUSUAL SITUATIONS,

With a Brief Review of the Literature of Giant-Cell Formation.

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The object of this communication is to report four instances in which giant cells occurred in unusual situations and to bring together in this connection some of the more important literature relating to giant-cell formation.

Accordingly to the circumstances under which giant cells are found, we are accustomed to recognize three main groups: the myeloid type occurring in normal bone marrow and in sarcoma, the Langhans giant cell, characteristic of tuberculosis, and the foreign body giant cell. Upon morphological grounds, however, the latter two groups might be brought on account of the mural arrangement, in most cases, of their nuclei, into a single group, as distinct from the myeloid type, in which the nuclei are distributed irregularly throughout the cell. While finally, if function is considered, it is evident that all may be brought in a single group: that of cells having a destructive action more or less analogous to that of phagocytic cells. This function of the myeloid giant cells of the bone marrow, also known as "myeloplaxes" (Ziegler) and osteoclasts is well recognized, as it is also of the general group of multinucleated cells found about a great variety of foreign particles and the remains of tissue destruction. Concerning the Langhans type, although the evidence is not so clear, there is much to indicate that they may have a similar function.

Despite the fact that much has been written concerning the origin and nature of giant cells, there is little uniformity of opinion. The type of giant cells which has aroused the greatest interest and discussion, in this regard, are those occurring in the lesions due to the tubercle bacillus.

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In regard to the formation of these cells, we have two principal views: that of the French school, led by Metchnikoff, and that of the German school, consisting of Weigert and his adherents, among whom are, Baumgarten, Marchand and Klebs. Both schools hold that the giant cells develop from large formative cells, but there is a difference of opinion as to the nature of the cells. Metchnikoff claims that they are of leucocytic parentage, while Weigert thinks they spring from connective tissue or endothelial cells. Again their method of development gives rise to differing views. Some authorities hold that the individual cells, from which the giant cells develop, group themselves around masses of bacilli and become fused, without division of their nuclei. Opposed to this is the view of Weigert, who thinks that they are formed by amitotic or direct division of a single nucleus and cell. Metchnikoff states that giant cells thus formed have ameboid movements and are phagocytic, in that they digest and otherwise remove the tubercle bacilli. On the other hand we have positive assertions that the multinucleated masses possess neither ameboid nor phagocytic qualities. The difficulty does not end here, for different views are also held in regard to the nature of the cellular cytoplasm. Weigert and his associates insist that the central cytoplasm is in the process of necrosis, the nuclei being placed in the more vital parts of the cell. Metchnikoff thinks that the centre of the cell, although appearing necrotic, is especially active, the nuclei being grouped in the less active parts. In other words it is Metchnikoff's opinion that the giant cells of tuberculosis are living and defensive cellular masses, while Weigert is convinced that they are the seat of a progressive necrosis and are without function.

Koch is one of the few Germans whose views do not differ in every respect from those of Metchnikoff. He regards the giant cells as being permanent structures possessed of more vitality than the bacilli which they contain; he says he has seen many cells containing degenerated forms of bacilli, which he contends have been destroyed by the cellular protoplasm. He thinks that the tubercle bacillus on its entrance into the organism is first attacked by the "microphages" or polymorphonuclear leucocytes; these are later joined by the "macrophages" which develop into epithelioid cells and which in turn form giant cells. In experimental tuberculosis he found giant cells containing bacilli, which from their staining characteristics and morphology, were evidently degenerated forms; this degeneration being due to changes brought about by the cells containing them. Miller is also convinced that the included bacilli undergo degeneration, for the reason that he has seen many of them colored black with osmic acid. Shüppel and Ziegler found various concentric, lamellated, calcareous, concretions in the interior of tubercle giant cells. These formations Metchnikoff regards as the result of the calcification of the tubercle bacillus in the interior of the cells, and a step in the process of the reaction of the giant cell against the contained bacillus.

Stschastny and Welcker also found degenerated forms of the tubercle bacillus in giant cells in experimental tuberculosis of the rabbit and guinea pig. Unna disagrees with Metchnikoff's view, that degeneration of the included bacilli is an indication of the phagocytic power of the

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enveloping cell. He attributes this degeneration to the poisonous agent which has paralyzed the affected parts of the cell, and not to any activity of the giant cell itself.

Weigert, in direct opposition to Metchnikoff, Stschastny and Welcker, says that the forms, which the latter claim to be degenerated bacillary bodies, are merely artefacts, or else particles of a granular material having no relation whatever to the tubercle bacillus.

It is apparent that the question of the origin and nature of the tubercle giant cell is no nearer a satisfactory solution than it was when Langhans first suggested the theories of progressive nuclear division of cellular confluence. It seems, however, to be generally agreed that the cells, which either by confluence of the protoplasm or by nuclear division, give rise to the multinucleated masses, are those to which the name epithelioid has been given.

Before the discovery of the tubercle bacilli by Koch it was held by many, that the giant cell of tubercle owed its origin to metamorphosed blood vessels, but of late years this view has been practically abandoned for lack of supporters. In tuberculosis of the liver, Klebs thinks that many of the giant cells there found, are formed from the lining epithelium of the biliary ducts. A somewhat similiar view is held by Arnold, who in miliary tuberculosis of the kidney and liver, found giant cells which were formed apparently by the confluence of neighboring epithelial cells lining detached portions of urinary tubules and bile ducts.

In connection with the giant cells of tuberculosis, Hektoen's studies have added greatly to our knowledge of the fate of these masses. He concludes that in the healing of non-degenerated tuberculosis tissue, the multinucleated giant cells may either disintegrate and subsequently become absorbed, or may divide again into smaller cells. The latter occurs more frequently. Under certain conditions after thus separating into smaller cells they may undergo progressive changes. This leads him to doubt the theory of Weigert and others that giant cells are necrobiotic elements doomed to destruction, and to support the teleological view held by Metchnikoff, that they are defensive plasmodia, in that they engulf and destroy the tubercle bacillus.

Unna in his work on the histopathology of skin lesions discusses at considerable length the nature of the giant cells found in lupus. He believes that the bacilli within the giant cells elaborate a poison which paralyzes certain parts of the cell. In the neighborhood of the nuclei this poisonous action is not only resisted, presumably as a result of nuclear influence, but the nuclei proliferate and elaborate an antitoxic substance which neutralizes the action of the bacterial poison. While nuclear proliferation lasts, he concludes, there can never be complete necrosis of the giant cell.

Concerning the foreign body giant cells which may readily be studied experimentally a large mass of literature is at hand. As their function appears to be to remove dead and useless fragments of tissue, or to surround and render innocuous particles of extraneous matter which have found their way into the tissue, they are seen under a great variety of conditions. The substances most frequently enclosed by them are bits

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of hair, degenerated or cornified epithelium, cholesterin and fatty acid crystals, old pigment of the blood, extraneous insoluble particles, sutures, etc. To quote a few specific examples of but one type, suffice it to state that LeCount has described cholesterin giant cells in an old hydrocele, Meyer in foreign body peritonitis, Manasse in polypoid growths of the middle ear, Cramer and Schultz in a tumor of the eye and Ruge and Kruchman in sebaceous cysts.

One of the most interesting studies of foreign body giant cells is the experimental investigation of Faber. He introduced agar into the subcutaneous tissues of rabbits and observed the changes which followed. After various intervals he found about the particles of agar, leucocytes, epithelioid cells and giant cells. He found that the latter not only surrounded the small masses of agar but also sent processes into their substance. In some of his experiments he used agar impregnated with Berlin blue, and thus was able to obtain positive evidence that digestion was really taking place within the multinucleated cells, for it was easy to demonstrate that in such cells, in addition to the larger masses of foreign material, were many fine colored particles which had been broken off from the former in the process of its digestion. Indeed he saw some cells which contained only particles of Berlin blue and no large agar clumps.

Other experimental investigations have yielded similar results. Among the substances used in the experimental studies are small particles of sterile sponge, catgut, bits of glass, pollen grains, lycopodium spores and coagulated blood serum.

There are almost as many theories concerning the origin of these foreign body giant cells as there are writers dealing with the subject. Many authorities have reached the conclusion that the cells which take up foreign bodies are proliferating fixed tissue cells. Langhans in 1868 in his elaborate discussion of the subject originated the first theories as to giant cell formation, and, although somewhat modified, these still hold to-day. He suggests two possibilities: (1) that they may arise from a single cell by multiplication of the nucleus, or, (2) they may result from the fusion of many cells into one. To the former Dürck has given the name "proliferation giant cell" and to the latter "conglutination giant cell." Ziegler says that if the formation of giant cells is associated with an inflammatory reaction and if the proliferating tissue contains leucoctyes, the latter may develop into giant cells by a division of their nuclei and act as phagocytes. Several German writers hold that it occasionally happens that mononuclear cells take up small foreign bodies into their substance and through continued nuclear division become converted into giant cells. Virchow concluded that foreign body giant cells were altered lymph vessels. Koster thought they came from the endothelium of blood vessels. Of late years, however, investigators have been in general accord in denying the vascular origin of the multinucleated cells, although one or two recent writers have brought forward the theory again. Weiss, who made a thorough study of this subject, concluded that the giant cells which he found surrounding foreign bodies were always formed by the confluence of the protoplasm of neighboring

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cells, the latter being in most cases "granulation cells." Faber, as the result of his experimental subcutaneous introductions of agar, is positive that the giant cells which he noted were formed by the merging together of numerous epitheloid cells. Goldman regards the multinucleated cells which form around hairs in a dermoid cyst as arising from a single polymorphonuclear leucocyte by the division of its nucleus. On the other hand Buxton says that the leucocytes of the early invasion do not give origin to foreign body giant cells for several reasons: (1) because the latter are not seen until granulation tissue has begun to form, (2) their formation begins at that point of the foreign body which is nearest to the granulation area, and (3) in general their appearance both as regards nucleus and protoplasm closely resembles that of epithelioid cells. Marchand concludes that the cells in question are formed from epithelioid cells, which in turn develop from the endothelium of capillary blood vessels, thus indirectly returning to the views of Virchow and Koster that they arise from blood vessels.

Observation No. 1.—Multinucleated cells within the bronchi in bronchiectasis.

(Records of the Pathological Department, University of Pennsylvania, No. 01.46.) Autopsy by Dr. Pearce. Clinical Diagnosis:*—Pulmonary tuberculosis and pneumonia.

Anatomical Diagnosis.—Chronic interstitial pneumonia (diffuse); acute lobar pneumonia (right upper lobe); bronchiectasis, emphysema; general arteriosclerosis; chronic mitral and aortic endocarditis; hypertrophy of left ventricle; general chronic passive congestion; congenital hypoplasia of right kidney; compensatory hypertrophy of left kidney; chronic fibrous peritonitis; chronic fibrous pleuritis.

Lungs.—The lungs are smaller than normal and very firm. Posterior surfaces are covered by adhesions. On section there is seen a very definite diffuse increase of connective tissue. Throughout both lungs, but more especially in the lower lobes, are many closely set, minute cavities, apparently dilated bronchi, containing a thick mucus which is adherent to their walls. About these the new formation of connective tissue is very evident and often takes the form of grayish tubercle-like masses. There is a well marked dilatation of the air vessels throughout the lungs, especially along the anterior edges, where small blebs 2 to 3 mm. in diameter may be seen. The right upper lobe is prominent, of a grayish red color and completely solidified. On section it is grayish red in color, finely granular, and on pressure a large

*For the autopsy notes from which this abstract of gross findings is taken I am indebted to Prof. Allen J. Smith, of the University of Pennsylvania.

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amount of yellowish-gray fluid escapes. In the midst of this solidification is a dilated bronchus 1.5 cm. in diameter. The bronchi contain a large amount of grayish yellow, and in some places, slightly greenish mucus disagreeable in odor.

Histological Examination.—Throughout all portions of the lung the air cells are largely obliterated and replaced by a very dense and very vascular connective tissue containing many lymphoid and plasma cells. In this tissue is a moderate deposition of carbon pigment. Special stains show it to be unusually rich in elastic fibres. The air cells which remain are enlarged. The bronchi, with the exception of the larger structures are for the most part greatly dilated and present very irregular outlines. In short the condition present is a chronic interstitial pneumonia with emphysema and extreme bronchiectasis, and, as the chief interest lies in the giant cells within the bronchi, the latter structures only will be described in detail.

Of the smaller bronchi a few are of normal diameter and some are collapsed, but for the most part they are greatly dilated. Their walls are greatly thickened and the mucosa irregular and convoluted. Into some the newly formed connective tissue has sent finger-like projections, these causing more or less invagination of the mucosa. The epithelium of the smaller bronchi is not infrequently separated from the underlying structures and thrown into reduplicated folds. The cells of these smaller tubes are of the low columnar type and stain deeply with hematoxlyin. Not infrequently they penetrate in an irregular manner the surrounding tissue. All the bronchi with the exception of the very largest are partially filled with masses composed mainly of a thick hyaline mucus, with, in addition, polymorphonuclear leucocytes, epithelial cells and cellular detritus and a few red cells. The mucus which holds the mass together has in places a more or less fibrillated appearance, suggesting a fibrin network; elsewhere it is homogeneous. In the center or at the periphery of many of these masses are seen one or more large multinucleated cellular masses which vary considerably in appearance. In outline some are almost spherical, while others are very irregular or elongated. The irregularity is never so great as to suggest the presence of cell processes similar to those of the tubercle giant cell. The nuclei range in number from 2 to 80 or 100 and are oval and vesicular; the nuclear chromatin appears very plainly and takes a blue stain with hematoxylin, while the proto-

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plasm stains a light pink with eosin. Many of the cells are vacuolated and the vacuoles contain in many instances a poorly staining granular material, the nature of which cannot be determined.

The nature and mode of formation of these multinucleated cells cannot readily be determined. A careful review of the literature reveals no mention of similar cells under like circumstances. They are not a manifestation of the lesions of tuberculosis or syphilis, and it cannot be shown conclusively that they are foreign body giant cells which have formed about mucus or detritus in the bronchi, though the occasional occurrence of crystal-like fragments within their protoplasm suggests such a possibility. As this possibility, however, presupposes the conglutination of proliferation of desquamated epithelial cells it is hardly worthy of consideration. It is, however, evident that they must in some way have been formed from the epithelium of the bronchi. Careful study of many preparations has shown that not infrequently small masses of the cells forming the epithelial lining protrude in sprout-like processes into the lumen. These cells lose more or less their cylindrical form and constitute an irregular arrangement of nuclei without distinct cell outlines. It is possible that these cell masses could become constricted at their bases and finally separate entirely from the mucosa and by contraction form round or oval multinucleated cells resembling giant cells, which in the fluid of the bronchi might retain for some time their normal staining characteristics. Such a mode of origin, however, cannot be demonstrated.

The possibility that these cells are but the tips of budding processes separated by the knife from the cell strands connecting them with the underlying mucosa, and therefore analogous to the multinucleated masses seen in the placenta, has been considered. A study of serial sections, however, has shown this not to be the case.

That giant cells commonly arise from epithelial cells is doubtful, but that they may do so is evident from a number of investigations. In tuberculosis of the intestine, Gaule thought that some, at least, of the giant cells originated in the epithelial lining of the tubules. Similarly Klebs and Arnold, as stated above, in tuberculosis of the liver and kidney, thought that the existing giant cells were formed from the lining epithelium of the bile ducts and the uriniferous tubules. Pearce in his study of experimental cirrhosis of the liver, found multinucleated masses, essen-

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tially foreign body giant cells, since they were active in removing necrotic hyaline liver cells. These he declares are derived in part from endothelial cells and in part from liver cells. C. Friedländer, in a peculiar form of pneumonia to which he has given the name "Desquamative Hepatization," describes giant cells in the alveolar spaces, which he thinks originate from the lining of the alveola.

The occurrence of cells so typically of the giant cell type in such a place is so unusual that one hesitates to offer an explanation. It seems justifiable, however, in view of the fact that origin from either desquamated epithelium or the cells emigrating from the blood stream appears untenable, to conclude that they must be pinched off masses of excessively proliferating sprouts of the bronchial epithelium, which still retain more or less their natural staining characteristics.

Observation No. II.—Giant cells in a Carcinoma of the Tongue. *(Records of the Bender Laboratory, Surgical Path, No. 06-535.)*

The tumor was one involving the right half of the tongue, right tonsil and adjacent lymph nodes. It presented, except for extensive necrosis, the usual gross appearance and histologically was of little interest except for the presence of large numbers of multinucleated cells in and about necrotic epithelial pearls containing much kerato-hyalin. These cells lay in dense masses of lymphoid and plasma cells and in intimate contact with fragments of keratinized epithelial cells and oftentimes formed a perfect ring about smaller disorganized epithelial pearls. They had in some instances a round or oval outline, but the majority were very irregular, a considerable number sending elongated processes of their protoplasm into the surrounding tissue.

In the protoplasm many vacuoles are seen, some being free of all contents while others contain a variable amount of hematoxylin staining material. Not infrequently the material within the cells can be definitely recognized as fragments of degenerated epithelial cells. The vesicular nuclei, some of which are round, others oval, are situated as a rule at the periphery or at the poles, though an irregular arrangement is not uncommon. The larger cells contain 40 to 50 nuclei. There is no evidence of nitosis.

Concerning the occurrence of giant cells in epithelial tumors there is very little to be said.

In several cases of nævo-carcinoma, Unna describes giant cells, similar to those of tuberculosis in that their nuclei are

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peripherally placed. Malherbes and Chenantais saw similar cells in epithelioma of the sebaceous glands of the neck. Krauss in 70 cases of epithelioma found giant cells in 10. He also found them in an epithelioma of the clitoris and in several adenomata. In an epithelioma in which calcification had taken place, Denecke also saw such cells. Krüchman observed them in carcinomata of the eyelid and of the œsophagus. Becher found multinucleated cells in several cases of lipoma and carcinoma of the upper and lower lips. Delamare and Lècene, out of a total of 250 epitheliomas examined, saw giant cells in 14, the majority being found in squamous cell carcinoma of the tongue, cheeks, larynx, œsophagus, tonsil, gums and cervix. Cramer and Schultz noticed similar cells in a pseudoglioma of the retina.

In some cases, as in the one here reported, the giant cells are scattered throughout the area of round cell infiltration and in close proximity to the masses of cornified epithelial cells or so-called "pearls." This association has suggested the possibility that they represent an attempt to remove the new growth and bring about a spontaneous healing. This question has been answered affirmatively and negatively by both French and German writers. That giant cells can surround and remove vigorously growing cells is very doubtful, but that they may take a part in removing cornified epithelium or other inert material, as they do elsewhere in the body, is very probable. Becher even goes further than this and says that it is the function of the giant cell to bring about organization of the "epithelial pearls" and their spontaneous healing, making it possible for them to be replaced by connective tissue. Unna thinks that the presence of giant cells in carcinoma suggest some infectious agent as the causal factor. In this connection it may be recalled that Unna describes multinucleated cells in various of the more uncommon skin lesions. He found in Spiradenitis disseminata suppurativa, a diffuse inflammation of the sudoriparous glands, that the epithelial cells of the ducts become swollen, separate and sometimes form multinucleated masses which he thinks are typical giant cells. Although unable after examination to find any specific micro-organisms, nevertheless, from the nature of the lesion, he thought that the condition pointed to an inflammation of infectious origin.

Mibelli, in acne keloid, found giant cells around the hair follicles. This led Unna to consider that this disease also was

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caused by a distinct infectious agent the nature of which is unknown. In varicella, Unna also describes giant cells in the prickle cell layer of the epidermis, and on account of their peculiar form gave them the name "balloon" giant cells.

Observation No. III.—Giant Cells in a Recurrent Granulation Polyp of the Aural Canal. *(Bender Laboratory Records, Surgical Path. No. 06-332.)*

The gross appearance of the tumor, a small polyp, is of no special importance. Microscopically, it is in part necrotic with extensive leucocytic infiltration and in part composed of a matrix of newly-formed connective tissue with a small round cell infiltration. Here and there a slight amount of œdema is noticeable. Scattered throughout the latter tissue are a number of protoplasmic masses irregular in outline with no definite limiting wall and containing 3 to 15 oval, vesicular nuclei. The nuclei are arranged irregularly throughout the cells, in some, crowded together in the center, in others, at the poles or periphery. Many of these cells contain a granular material staining with hematoxylin and resembling epithelial debris.

The occurrence of giant cells in aural polyps has been reported several times. Krüchman describes one and Manasse nine cases of granulation polyp of the middle ear in which giant cells were found. Manasse decided that they are of foreign body origin and have nothing to do with the formation of the polyps as such. Since giant cells are very often found in chronically inflamed tissue we have no new condition here. They indicate probably the presence of foreign particles used in medication, or possibly desquamated epithelial cells or fragments of adherent cerumen.

Observation No. IV.—Giant Cells in the Wall of a Cyst of the Broad Ligament. *(Records of the Bender Laboratory, Surgical Path. No. 05-1304.)*

Macroscopically the specimen may be described as a cyst measuring 12 x 8 x 7 cm. with areas of subcapsular hemorrhage. The walls are quite thick and firm in consistence and the contents a dark brown mucoid fluid in which are mingled brownish friable masses. In several places the wall of the cyst is irregularly thickened and contains minute cysts.

Microscopic Description.—Sections through the cyst wall show two zones. The outer consists of old fibrous connective tissue with a large number of small blood vessels. The inner is

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composed of young granulation tissue with its new blood vessels and small accumulations of leucocytes. Scattered profusely throughout this granulation tissue are small, round, oval or irregularly shaped hyaline masses, many of which are surrounded by multinucleated masses of protoplasm. These latter are of various shapes and sizes corresponding to the enclosed material. The nuclei are of the oval vesicular variety, the larger cells containing from 50 to 100. These nuclei are also varied as to their situation, some being massed in the center, a few at the periphery, while others are arranged at one or either pole. The enclosed material is apparently of a mucoid nature, which it would appear has become adherent to the granulating surface and surrounded in the process of repair, with the ultimate formation of giant cells about the less soluble particles.

It is interesting to note that in 1870 Langhans noticed somewhat similar phenomena about extravastated blood or blood introduced as a coagulum into the cutaneous tissues of various animals. In each instance the fluid portion of the blood was soon absorbed. Around the remains of the clot he saw multinucleated giant cells and was positive in asserting that absorption was due to the phagocytic action of the latter.

A few cases of giant cells found in connection with cyst formations have been reported by German writers. Goldman and F. König describe multincleated cells in the walls of dermoid and atheromatous cysts, Bohm in a traumatic epithelial cyst, and Kühne in a cyst of the œsophagus.

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SPONTANEOUS AMPUTATION OF AN APPENDIX VERMIFORMIS CONTAINED IN A FEMORAL HERNIA SAC.

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(*From the Bender Laboratory, Albany, N. Y.*)

Within the past few years and especially since the time when the radical cure for hernia became customary, a large number of cases of hernia have been reported in which the appendix alone or accompanied by omentum, or omentum and intestine have been found occupying the sac. Previously, only isolated cases appear in the literature. Probably the first reported was that of Morgagni in 1751. Piersol, in 1901, collected 125 reported cases, and since that time a number of communications have appeared in rapid succession, describing instances of appendices found in the various hernial sacs, the greater majority being

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found in right-sided herniae, especially the inguinal form. Edington, Bidwell, Eccles, Keetley and Southan have described cases in which the appendix was the sole occupant of the sac.

Most of the cases have been found at operation, while a few have been accidentally found at autopsy. It is now known that the appendix is present in about one or two per cent. of all hernias.

Hernia of the appendix may be either congenital or acquired. According to Hutchinson all the congenital cases are right sided and of the inguinal form. In the acquired forms the usual causes of hernia, as general enteroptosis together with the unusual mobility of the appendix are the main etiological factors. It is more common in children and advanced life than in early adult and middle age. According to Rivet's figures seventy per cent. occurred in men and thirty per cent. in women. The inguinal form constitutes seventy to eighty per cent. of all cases; the femoral twenty to thirty. Of the fifty-three cases of strangulated appendix in a hernia sac recently collected by Clogg three only occurred in males, and of these three, two were infants. Both were inguinal hernias—fifty occurred in women and in each instance the hernia was femoral.

Pathological conditions of the herniated appendix, especially those of an inflammatory nature, are not uncommon. "The tendency to inflammation of the appendix is greater than in the unherniated organ" (Jopson) and irreducibility, according to Bararde's statistics, is almost the rule. In his ninety-seven cases inflammation was found in thirty and strangulation in forty-seven. In many instances the symptoms supposed to be due to a strangulation of the hernia have been found to be due to an inflamed or gangrenous appendix, which had become adherent to a hernial sac. Eccles states that the inflammation of the appendix in these cases takes place after its prolapse into the hernial sac, and that the strangulation is secondary, being caused by an acute inflammatory process taking place in a confined space.

Kleberg describes a most interesting case in which the appendix was found in a left-sided hernial sac at operation. After having made the incision he noticed a gangrenous piece of tissue which later sloughed off, and was described by the pathologist as appendiceal tissue. Shaw and Stanton describe a case of hernia of the appendix in which the appendix was found to be intimately

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attached to the epididymus. Wölfer and McArthur each report a case of cystic appendix in the sac of a hernia and Wood has called attention to the danger of rupture by taxis when a cystic appendix is in an inguinal hernia. Such an accident is reported by Van Hook. Various other interesting conditions of the inherniated appendix are possible, but all may be summed up by stating that conditions which may affect the appendix when in its normal position may affect the appendix also when within a hernia sac. We can find, however, no reference in the literature to the spontaneous amputation of an inherniated appendix and for this reason feel justified in placing on record such a case although the condition must be considered more as a curiosity than as one of clinical or pathological importance.

Case Report.—Mrs. M. E. G., aged 80, housewife, entered the Albany City Hospital, service of Dr. A. W. Elting on March 9, 1906. The family history is negative.

Past History.—The patient first noticed a small lump in the right groin about eight years ago. This swelling gradually increased in size until it reached the size of a goose egg and was recognized as a hernia. At first it gave rise to no symptoms, but later, on the entrance of a portion of the intestine into the sac, the patient would have a feeling of weight and suffer extreme pain. She was able at such times to reduce the hernia and would then be relieved. She has worn a truss for the past three years. The rupture "comes down" about every six or eight months.

Present Illness.—The patient felt perfectly well until she was taken with slight pain in the right groin, which increased in severity until it was so severe as to be intolerable. She did not vomit. The bowels were constipated and the hernia irreducible.

Operation.—With the patient in dorsal recumbent posture there presented a sausage-shaped tumor, well down in groin on the right side, which measures about 8.5 x 3.5 cm. An effort was made at reduction while on the table, but without avail. An incision was made over the tumor mass parallel with Poupart's ligament and the tissues separated and the hernia sac exposed. The sac was opened and found to contain three to four inches of ileum markedly congested and almost black. The neck of the sac was very tight, being of the size of a finger, and it was necessary to incise the constricting band somewhat. Some hot saline solution was poured on the gut and the color began to return with contraction of muscular fibres. The gut, after considerable effort, slipped back into the abdomen. What was considered as a properitoneal lipoma was attached to the inner surface of sac. On close examination of this mass was found what appeared to be a rather short obliterated appendix with smooth ends and without caecal attachment, which had apparently been amputated by pressure. To this was attached a definite mesentery. A considerable tongue of omentum was deligated along the sac. The patient made an uninterrupted recovery.

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Gross Description of Specimen.—Attached to an apparently smooth serous membrane (hernia sac) measuring 3.5 cm. in diameter is an irregular mass of adipose tissue closely resembling that of the meso-appendix. Attached to this mass and slightly imbedded in it is a cord-like structure which measures 4 cm. in length and 0.5 cm. in diameter. Its surface is smooth, glistening, pinkish gray in color and it is rounded off at both ends. To these ends are attached by fibrous bands small masses of adipose tissue. Adherent to the hernia sac at its under surface by a long fibrous band is a piece of omentum containing considerable fat. *Anatomical Diagnosis.*—Hernia sac containing omentum and a portion of an appendix (spontaneous amputation).

Histological examination of the appendix shows the lumen to have been entirely obliterated and the mucosa completely replaced by fat and connective tissue containing a few lymphoid cells. The musculature is slightly atrophic, and there is a light infiltration of lymphocytes and eosinophiles. The peritoneal coat here and there shows many small hemorrhages. That the structure is appendix and not some other obliterated tubular structure or ligamentous mass is definitely determined by the character and arrangement of its outer coats. *Microscopic Diagnosis.*—Chronic obliterative appendicitis.

The only problem of pathological interest in this condition is the question of the sequence of the obliteration and amputation. It seems most probable that the obliteration of the appendix had occurred before the organ entered the sac, though of course it is not possible to exclude a gradual obliterative appendicitis occurring after its entrance. Under either circumstance it would appear to be quite certain that the amputation was due to the gradual constriction of the proximal portion of the appendix between the divisions of the fascia lata forming the boundaries of the femoral opening, this force being aided in part perhaps by the pressure of the truss. That the constriction leading to amputation as primary, or due to an acute inflammatory condition causing adhesions about the proximal portion of the appendix, appears very improbable, for under such circumstances we would expect either a cyst or empyema of the listal portion of the organ, or perhaps even necrosis, but certainly not an obliteration unless the adhesions involved the appendix throughout its entire length and on all sides, which was not the case.

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EXFOLIATIVE CYSTITIS. A CASE REPORT.

BY J. FLETCHER ROBINSON, M. D.,
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(*From the Bender Laboratory, Albany, N. Y.*)

The literature of affections of the bladder offers so few examples of cystitis with exfoliation of large portions of the bladder mucosa, that it appears justifiable to report a condition of this kind recently observed by the writer. The expulsion of a part or the whole of the mucous membrane of the bladder occurs more frequently in women, though it may be seen, rarely, in men. It is usually associated with a cystitis occurring during pregnancy, or as the result of catheterization and irrigation. Boldt,[1] after a study of a few cases of his own and of several collected from the literature, concludes somewhat as follows:

Exfoliative cystitis is often associated with a retroverted pregnant uterus and usually manifests itself at the third or fourth month. About 50 per cent. of the cases are due to this cause. Other causes are, a retroverted myomatous uterus, the pressure made by a myoma choking the pelvis, retention of urine or the instillation of very strong, irritating solutions. The common factor underlying all the various causes is probably the ischemia produced by pressure, for cutting off or lessening of the vesical blood supply results in ischemic necrosis with or without infection. The caustic action of the ammoniacal urine in long-continued distention of the bladder may also play a part.

Exfoliative cystitis usually begins with abrupt onset. The detached membrane may be extruded entire or in small pieces; the mucous surface may be so altered by the necrotic changes that it is recognizable with difficulty, and its surface is often studded with uric acid crystals. Adhering to it are often more or less extensive portions of the muscular coat, and in the worst cases the peritoneal coat is also involved.

The prognosis is usually favorable except in those cases associated with sepsis. The treatment is usually that adopted for cystitis after correcting any displacements that may be present, and restoring the blood supply as nearly as possible to normal.

[1] Boldt, *Am. Jour. of Obst.*, 1888, xxi, 361.

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Dawson[1] reports a case of exfoliation of the bladder mucosa in a colored woman, the entire mucous membrane being passed *en masse* from the urethra

Norris[2] mentions a similar condition in a patient aged thirty-two, due to a virulent infection by the colon bacillus. As the acute symptoms subsided, two ounces of a five per cent. solution of silver iodide were introduced into the bladder once a day at the conclusion of irrigation. The patient improved slowly. After two weeks of treatment she was permitted to go home and was ordered to return on alternate days for treatment, but neglected to do so. One week after her discharge she returned with her urethra blocked by a sloughing mass as thick as a lead pencil, four inches of which were outside the external urinary meatus. The bladder was distended and the patient had been unable to pass urine for fourteen hours. With some difficulty an entire cast of the bladder was removed, followed by a gush of urine. Microscopic examination revealed portions of adherent muscularis. The entire specimen was undergoing necrosis.

H. C. Cochan[3] observed in a woman four months pregnant a distention of the bladder to within an inch of the ensiform cartilage, accompanied by detachment and expulsion of the entire bladder mucosa. The cast was so perfect that openings corresponding to the ureteral orifices could be readily seen. The patient was able to leave the hospital in twenty days and recovered completely.

Schabert[4] reports a case following the birth of twins.

In a case mentioned by Kelly,[5] an over distention of the bladder followed ovariotomy and portions of the mucosa were cast off.

To these reports which, though they by no means cover the entire literature represent the more important types of exfoliation, I desire to add the following:

A folded and flattened membranous mass, preserved in alcohol and resembling in a general way in color and consistence a piece of folded gutta percha membrane, was sent by Dr. I. L. Goff of Howard, N. Y., on June 16, 1906, to the Bender Laboratory with a request to determine its nature.

[1]Dawson, *Johns Hopkins Hospital Bulletin*, 1898, ix, 155.
[2]Norris, *American Medicine*, 1906, xi, 478.
[3]Cochan, *Medical News*, 1888, lxiii, 633.
[4]Schabert, *St. Petersb. med. Woch.*, 1902, xix, 373.
[5]Kelly, Operative Gynecology, New York, 1906.

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The accompanying letter stated that the patient from whom it was obtained was being treated for cystitis and had passed this substance from the urethra. The specimen, after being softened by immersion for some time in salt solution and spread out, may be described as a thin brownish yellow, irregular disk, uniform in thickness, translucent and slightly elastic and about six cm. in diameter. Microscopic examination of small portions imbedded in celloidin and stained with haematoxylin and eosin showed several imbricated layers of squamous epithelial cells arranged as are those of the normal bladder mucosa. These cells are in part necrotic and show no leucocytic infiltration. No subepithelial structures are present.

From notes furnished by Dr. Goff the following brief history was obtained. The patient, a married woman of about 40 years of age, a schoolteacher by occupation, had had two previous attacks of cystitis. During the attack characterized by the exfoliation here described she was under treatment for about one week, receiving internally, salol, acetate of potash and fluid extract of corn silk with sufficient codeine to relieve the pain. Hot normal salt solution irrigations was used at first, and later a solution of boric and tannic acids and morphine as hot as could be borne. The bowels were kept open with salines. Recovery was rapid, and no recurrence was reported. There had been two previous attacks, which were mild and unaccompanied by any exfoliation of mucous membrane.

In view of the scanty history it is impossible to arrive at any definite conclusion concerning the cause of the exfoliation. The absence of leucocytic infiltration in the material examined and also of any record of an examination of the urine forbid a statement concerning the presence of an inflammatory condition. The absence of pregnancy rules out one of the usual causes. The solutions used for irrigation are not such as usually cause injury, though Boldt quotes a case of Begonin's in which exfoliation was due apparently to the use of normal salt solution. It is possible that very hot solutions might cause necrosis and exfoliation of the mucosa, but in this instance there is no evidence that the irrigation caused the patient discomfort, as would necessarily be the case under such circumstances.

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MALARIA WITH GENERAL DISTRIBUTION OF THE PLASMODIA.

By ARTHUR T. LAIRD, M. D.,
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(*From the Bender Laboratory, Albany, N. Y.*)

Records of the microscopic study of the lesions of malarial infection are, as stated by Ewing,[1] not very numerous, and much yet remains to be learned of the parasitology of the disease from microscopic studies of the visceral lesions. It has therefore seemed worth while to report the following case in which large numbers of the parasites were found in many of the organs and tissues.

*Bender Laboratory Records, Autopsy No. 535.**

Anatomical Diagnosis.—Pernicious malaria with general pigmentation most marked in the liver and spleen. Marked enlargement of the spleen. Hematogenous jaundice. Submucous hemorrhages of the stomach. Pigmentation of the mucous membranes of the stomach and intestines and of the pancreas. Cloudy swelling of the kidney, liver and heart. Chronic pleuritis (left). Hypostatic congestion and slight oedema of lungs. Atheroma effecting the bases of the mitral and aortic valves and the aorta and coronary arteries. Grayish pigmentation of the cortex of the brain. Presence of malarial parasites in the capillaries throughout the body.

The *skin, serous* and *mucous membranes,* including the conjunctiva are all very yellow, as are also the fatty tissues generally.

Liver.—27 x 16 x 10 cm. The capsule is smooth and of dark color. On section it is slate gray in color with indistinct markings. No necroses are seen. The gall-bladder measures 3.5 x 1.5 cm. and contains dark viscid bile. The bile ducts are patent.

Spleen.—6.5 x 5 x 2 cm. The capsule is smooth and free from adhesions. On section the organ is firm in consistence, deep purple in color, with prominent Malpighian corpuscles.

Kidneys.—Both are about the same size, approximately 11 x 6 x 4 cm. The capsule strips with some difficulty, bringing with it portions of the kidney substance, yet the surface for the most

*No clinical history could be obtained. The subject, a traveller, passing through Albany, was found dead by the hotel attendants. At the request of the coroner the autopsy was made by the writer. Only the anatomical diagnosis and those changes apparently due to malaria are given in the description of the autopsy.

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part is smooth. On section the organ is firm and lighter in color than normal. The cortex is narrow.

Pancreas.—Measures 18 x 3 x 1 cm. On section it is bluish gray in color, otherwise appears normal.

Stomach.—In the mucous membrane of the stomach are numerous pin-point hemorrhages covering an area of 10 cm. in diameter.

Intestines.—The mucous membrane of the small and large intestines is slate gray in color.

Brain.—There is grayish pigmentation of the cortex of the brain.

Microscopic Examination.—Fresh smears made at the time of the autopsy from the *brain, bone marrow* and *spleen* show numerous intracellular parasites. These usually have the form of small spheroids, staining blue and enclosing coarse masses of brownish black pigment. In the larger forms the pigment is more scattered and finer grains are seen. No ring bodies, rosettes or crescents are found.* Sometimes a red cell contains more than one parasite. Phagocytic cells containing pigment are also seen.

Sections of various organs after Zenker and alcohol hardening were studied.

Spleen.—The pigment deposit is very extensive. Much of it is in dense masses within large phagocytic cells. There is cellular hyperplasia of the pulp tissue and the sinuses are choked and obliterated by pigmented cells. The nonpigmented cells of the Malpighian bodies stand out prominently. A very large proportion of the red cells of the pulp contain pigment or parasites. Pigment is also found within the leucocytes. The large phagocytic cells referred to are mono-nuclear, where a nucleus can be made out.

Liver.—The parasites are very numerous. They are englobed in free red cells in the capillaries or, more often, enclosed in large phagocytes together with degenerated parasites, red cells more or less degenerated, and pigment in the form of large brownish black masses and fine brownish grains. The large phagocytic cells are mono-nuclear, some of them are combined in the large protoplasmic masses described by Ewing. These fill and distend

*Parasites seen in fatal cases of acute malarial infection are only very rarely of the tertian type. Italian observers have claimed that tertian malaria is never fatal. Ewing has however reported a case. The aestivo-autumnal parasite is the one usually found and the one probably present in this case through this could not be demonstrated.

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certain of the capillaries. The parasites are very much more numerous in the capillaries, nearly every red cell in which is infected, than in the larger vessels where only comparatively few of the red cells contain pigment. The liver cells show albuminous degeneration. In many of them are seen numerous fine yellow granules very different in appearance from the malarial pigment. No typical malarial pigment is found in any of the liver cells.

Bone-marrow.—The cellular hyperplasia is marked, comparatively little adipose tissue being seen. The pigment deposit is extensive but not as marked as in the liver and spleen. The pigment is found especially in large mono-nuclear cells, in the form of dense circular and irregular masses and in fine granules. A larger proportion of the red cells are uninfected than in the spleen. Pigmented spheroidal bodies are seen which are probably free parasites. Here as elsewhere no ring forms, rosettes or crescents are found. No infected nucleated red cells are seen. Eosinophilic myelocytes are numerous. The changes in the bone marrow are, in general, of the first of the two types of marrow changes described by Ewing.

Lymph Nodes.—The lymph nodes contain a moderate number of pigmented red cells. Various phagocytic cells containing pigment are also noted. Cellular hyperplasia is present and the sinuses are obliterated.

Lungs.—The capillaries here as in other organs contain immense numbers of the parasites. In many of them practically every cell is infected. The infected cells are massed in the capillaries, the larger blood vessels being comparatively free from them. Large phagocytic cells are seen distending certain of the capillaries. These cells contain masses of pigment and red cells more or less degenerated.

Cardiac Muscle.—The muscle cells show only cloudy swelling. Very large numbers of parasites are found in the capillaries. Phagocytic cells are few.

Kidney.—The intertubular capillaries contain moderate numbers of parasites. Phagocytic cells containing pigment are only rarely seen. The kidney cells show moderate degenerative changes of the albuminous type. Pigmented phagocytes and infected red cells are found in the Malpighian tufts.

Intestines.—Numerous parasites are seen in the capillaries in the mucosa and in those of the muscular fatty and connective

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tissues. In certain areas the epithelial cells are necrotic and there is an infiltration of round cells in the deeper layers of the mucosa. Occasional phagocytes containing pigment are seen in the capillaries.

Pancreas.—Here, also, are numerous parasites and many phagocytes containing large and small pigment granules. These are exclusively in the capillaries, no pigment being found in the parenchyma.

Brain.—Enormous numbers of parasites are found in the capillaries, nearly every red cell being infected. They are less numerous in the larger vessels. A few phagocytes containing pigment are seen.

The pathology of malaria is summed up by Mannaberg as follows: "The anatomic characteristic of acute malaria is melanemia. Microscopically this is evident in the greyish brown to graphite color of certain organs, as the spleen, liver, brain and kidneys. The pigment is found in parasites or in tissue cells (leucocytes, macrophages of the spleen, endothelial cells, marrow cells, more rarely in the parenchymatous cells of glandular organs as the liver). The distribution of the pigment in the internal organs is not uniform. It is found in the capillaries rather than in the large vessels. Dead substances like powdered glass or cinnabar if injected into the circulation distribute themselves uniformly, while bacteria show a predilection for certain situations and for certain organs. This seems to be true of the malarial parasite. The distribution varies in different cases." This is well illustrated in the study by Ewing of material collected at Camp Wikoff, Montauk Point, L. I. He reports nine cases with clinical histories and autopsies. He found that the distribution of the parasites in the internal organs was not uniform. In one case, for instance, no parasites were found in the brain, while a very abundant deposit of pigment was seen in the kidney; in another a very large number of parasites occurred in the viscera, generally, especially in the heart muscle. Still another showed a concentration of parasites in the central nervous system; in this case severe degenerative changes were present in the kidneys, though parasites were absent from the renal vessels. One case showed localization of parasites in the bone marrow.

It is generally believed that in typical cases the spleen is the first seat of malarial infection. This is borne out by the results

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of Craig's autopsies on the bodies of individuals dead of latent malarial infection. In these the parasites were practically localized in the spleen and had not even been demonstrated in the blood during life, though careful search had been made. The liver showed melaniferous leucocytes, but no infected red cells. Saigol reports an autopsy in a case of malaria with congenital absence of the spleen. In this case the infection attacked the mesenteric lymph nodes, which showed marked hypertrophy. Hypertrophy of the suprarenal glands was also present.

Leonard Rogers has called special attention to the frequency of pigmentation, visible to the naked eye, of the mucous membrane of the small intestine. He found it to be present in fourteen out of twenty cases examined. He believes that the continued presence of the pigment in the mucous membrane eventually causes degenerative changes and appears to be a very important factor in producing the high mortality in malarial cachexia. In the early stages the villi show in addition to deposits of black pigment, a considerable degree of thickening and distortion produced by a cellular infiltration. Changes are also found in the deeper layers of the mucous membrane; in some cases the tube glands have nearly disappeared, while their place is taken by a dense cellular infiltration. On the other hand, the muscular layers show little change. The degree of loss of absorptive and secretory power of such a membrane must be considerable. In advanced stages the process goes on to the formation of fibrous tissue and the mucous membrane becomes much atrophied.

In the case here reported the parasites have a wide distribution, being found in practically every organ. The pigmentation is very marked in the spleen and liver and brain. The changes in the intestine are similar to those described by Rogers.

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BENDER HYGIENIC LABORATORY.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1906.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1906.

The Work of the Laboratory.—The routine examinations of all kinds are summarized in Table No. I.

TABLE No. I.—ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1905, TO AUGUST 31, 1906.

	State Department of Health.	City Department of Health.	Albany Hospital.	St. Peter's Hospital.	Child's Hospital and St. Margaret's House.	All other sources.	Total.
Autopsies	.....	.....	40	4	26	50	120
Surgical Specimens	.....	.....	1,040	280	10	141	1,471
Throat cultures	819	877	.....	.....	.....	18	1,714
Sputum	423	34	1	2	.....	72	532
Widal	150	.....	72	36	.....	39	297
Water, milk and ice	300	.....	.....	.....	.....	30	330
Miscellaneous	5	20	.....	.....	.....	63	88
Totals	1,697	911	1,173	322	36	413	4,552

This shows an increase over each of the preceding two years, of the work done for the Albany and St. Peter's Hospitals and for the City Department of Health, but a decrease in that done for the State Department of Health. There is also an increase in the number of examinations made for private individuals and the smaller hospitals. The total number of examinations is more than one-third greater than that for either of the two previous years. This increase has been mainly along lines of surgical pathology and clinical bacteriology.

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As this report marks the completion of the first decennial period of the existence of the laboratory, I have been interested in working out the amount of work done during this time. The results as given in the following table show a very satisfactory and definitely progressive increase in all lines of work. The figures are based on the examinations for each year ending August 31, and includes only those examinations of which we have records on file.

TABLE No. II.—TABLE SHOWING THE PROGRESSIVE INCREASE OF THE WORK OF THE LABORATORY DURING THE FIRST TEN YEARS OF ITS EXISTENCE.

	1897.	1898.	1899.	1900.	1901.	1902.	1903.	1904.	1905.	1906.	Totals.
Autopsies.....	63	66	93	92	117	123	114	123	129	120	1,040
Surgical Specimens.....	160	163	148	399	527	641	590	1,003	1,271	1,471	6,373
Bacteriology and Clinical Microscopy.....	441	367	335	789	1,595	1,977	2,120	2,515	2,683	2,961	15,783
Totals.....	664	596	576	1,280	2,339	2,741	2,824	3,648	4,083	4,552	23,195
Laboratory Courses.....	3	3	3	3	3	4	5	6	6	6	.....
Publications.....	2	7	8	9	10	3	8	11	8	17	83

Laboratory courses for undergraduates of the Albany Medical College have been given as follows:

1. Normal Histology.—Drs. Baldauf and Beilby, six hours a week.

2. Pathology and Bacteriology.—Drs. Pearce, Winne, Baldauf, Blackfan and Robertson, eight and a half hours a week.

3. Clinical Microscopy.—Drs. Laird and Frederick, five hours a week (class in two sections).

4. Surgical Pathology.—Drs. Elting, Carey and Sibley, two and a half hours a week.

5. Histology and Pathology, in connection with the course in Obstetrics.—Dr. Lipes, five hours a week (class in two sections).

6. Anatomy and Pathology of the Nervous System.—Dr. Archambault, one and a half hours a week.

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The only change during the past year in the conduct of these courses has been the division of the class in clinical microscopy in two sections, each section working on different days in order to allow more detailed instruction. The time devoted to the work in anatomy and pathology of the nervous system has been lengthened for the year 1906-07 to two hours. As the pathology of the nervous system will in the future be more fully covered in this course, the time given general pathology has been shortened to seven and one half hours a week, while the time devoted to normal histology has been limited to five hours. Both these changes were necessary also in order to give place in the schedules of the first and second years to the two courses in experimental physiology to be inaugurated this year under the direction of Dr. H. C. Jackson, and for which facilities are available only in this laboratory.

Among those who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are, Dr. D. C. Moriarta of Saratoga, Dr. Warren B. Stone and Mr. Rufus T. King of Schenectady, Drs. C. B. Hawn and J. D. Olin of Albany, Dr. J. S. Purdy of Auburn, Miss H. C. Acheson of Troy, Messrs. E. E. Tredway, J. F. Robinson, J. H. Linden, E. W. Fuller, R. P. Harris, N. K. Fromm, E. W. Jackson, G. S. Silliman and S. P. Brush of the Albany Medical College, and Mr. J. H. Musser, Jr., of the University of Pennsylvania. These have assisted in the routine work of the laboratory, pursued special lines of study or engaged in research work.

Investigations completed during the year are as follows:

1. McDonald, Ellice, Puerperal Infection; Report of Six Cases Illustrating its Varied Character. *American Medicine*, 1906, XI, 231.

2. Pearce, R. M., A Further Study of the Experimental Production of Liver Necrosis by the Intravenous Injection of Hæmagglutinative Sera. *Jour. Med. Research*, 1906, XIV, 541.

3. Pearce, R. M., Experimental Myocarditis; A Study of the Histological Changes Following Intravenous Injections of Adrenalin. *Jour. Exper. Med.*, 1906, VIII, 400.

4. Beilby, G. E., Affections of the Thyroid Gland; a Clinical and Pathological Study. *Annals of Surgery*, 1906, XLIII, 805.

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5. Pease, H. D., and Pearce, R. M., Liver Necrosis and Venous Thrombosis in Horses Actively Immunized with Diphtheria and Tetanus Toxins and Streptococci and their Products. *Jour. Infec. Diseases,* 1906, III, 619.

6. Pearce, R. M., Regenerative Changes in the Liver; A Study of Experimental Lesions in the Dog. *Jour. Med. Research,* 1906, XV, 99.

7. Macdonald, W. G., Practical Bacteriological Studies in the Surgical Clinic. *Surgery, Obstetrics and Gynecology,* 1906, III, 216.

8. Archambault, J. L., and Pearce, R. M., Tuberculosis of an Adenomyoma of the Uterus. *Jour. Am. Med. Assoc.,* 1906, XLVII, 768.

9. Pearce, R. M., and Baldauf, L. K., A Note on the Production of Experimental Vascular Lesions in the Rabbit by Single Injections of Adrenalin. *Am. Jour. Med. Sciences* (in press).

10. Baldauf, L. K., The Chemistry of Atheroma and Calcification (Aorta). *Jour. Med. Research* (in press).

11. Pearce, R. M., and Jackson, H. C., Concerning the Production of Cytotoxic Sera by the Injection of Nucleoproteids. *Jour. Infect. Diseases* (in press).

12. Jackson, H. C., and Blackfan, K. D., Action of Certain Drugs on the Elimination of Uric Acid During a Nitrogen-Free Diet. *Jour. Am. Med. Assoc.* (in press).

13. Schaible, F. G., Spontaneous Amputation of an Appendix Vermiformis contained in a Femoral Hernia Sac. *Albany Medical Annals* (in press).

14. Carey, H. W., A Note on Embryonic Glandular Tumors of the Kidney with Report of a Case. *Albany Medical Annals* (in press).

15. Fromm, N. K., A Report of Four Instances in which Giant Cells Occurred in Unusual Situations with a Review of the more Important Literature of Giant Cell Formation. *Albany Medical Annals* (in press).

16. Laird, A. T., Malaria with General Distribution of the Plasmodia. *Albany Medical Annals* (in press).

17. Robinson, J. F., Exfoliative Cystitis; A Case Report. *Albany Medical Annals* (in press).

Of these investigations, the second, third, sixth, ninth, tenth and eleventh were conducted under a grant from the Rockefeller Institute for Medical Research, and the twelfth under a grant

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from the committee on scientific research of the American Medical Association. Study number five was carried out in collaboration with the Antitoxin Laboratory of the New York State Department of Health.

Changes in the Staff.—Dr. L. K. Baldauf, first assistant for the past year, has been reappointed for the year 1906-7. Dr. K. D. Blackfan, after one year's service as assistant, has resigned, to take up general practice in Cambridge, N. Y., and in his stead Frank George Schaible (Albany Medical College, M. D., 1905) has been appointed. Dr. La Salle Archambault is continued as assistant in Neuropathology. Dr. H. E. Robertson, assistant in surgical pathology, resigned May 1 in order to accept a position as assistant resident pathologist at the Boston City Hospital, Boston, Mass., and to this position has been appointed John Fletcher Robinson (Univ. of Michigan, B. A., 1903, Albany Medical College, M. D., 1906).

The new position of pathological house officer to the Albany Hospital, created last year, was occupied first by Dr. William M. Dwyer, and later by Dr. F. G. Schaible. For the year ending May 30, 1907, C. W. Louis Hacker (Albany Medical College, M. D., 1905) has been appointed by the board of governors of the hospital.

Mr. Leonard M. Wachter, for several years assistant chemist and bacteriologist in charge of the Albany filtration plant, resigned on September 1st, to accept a position in the laboratory of the New York State Department of Health, and to this position, with the approval of the water bureau, has been appointed Mr. George Edward Willcomb (Massachusetts Institute of Technology, S. B., 1904).

Improvements.—The only important changes have been the alteration and equipment of a room for research work in physiological chemistry for the use of Dr. H. C. Jackson, and the installation of a one-half horse power electric motor and pump, in order to supply vacuum and air pressure for general laboratory purposes.

Gifts.—Through the generosity of Dr. W. G. Macdonald, one hundred dollars was placed at our disposal for the purpose of purchasing a polariscope. The great value of this gift is shown

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in the fact that the apparatus has already made possible the completion of an investigation otherwise impossible, and will in the future serve a useful purpose in both the teaching and the routine work of the laboratory.

The past year has been from every point of view the most successful in the history of the laboratory. The importance of our relation to the hospitals and physicians of this neighborhood, as well as to the community generally, is indicated by the large number and variety of our routine examinations. The teaching courses, now numbering six and next year to be increased to eight, have been most satisfactory, and the value of the facilities thus afforded the Albany Medical College are apparent. The quantity and quality of our research work, as indicated by the foregoing list of publications, will, I trust, appeal to you as of great value to the future, not only of the Bender Laboratory, but also to the medical school with which this laboratory is affiliated. With this evidence before you of the satisfactory fulfillment of all the functions of a laboratory, I earnestly recommend that every effort be made to obtain for the institution an adequate financial support, in order that its efficiency may not be curtailed or its development hindered.

RICHARD M. PEARCE,
Director.

September 1, 1906.

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STUDIES

FROM

THE BENDER HYGIENIC LABORATORY

ALBANY, N. Y.

REPRINTS

VOLUME IV

1907

PRESS OF
BRANDOW PRINTING COMPANY
ALBANY, N. Y.

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NOTE.

THIS volume comprises the publications of the Bender Hygienic Laboratory based on the work for the year ending August 31, 1907. Some of these have appeared in other journals, but for the sake of uniformity have been reprinted from the Bender Laboratory Number (January, 1908) of the ALBANY MEDICAL ANNALS. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY,
ALBANY, N. Y., *December*, 1907.

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STUDIES

FROM

THE BENDER

Hygienic Laboratory

ALBANY, N. Y.

REPRINTS

Volume IV

1907

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The Bender Hygienic Laboratory

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WILLIS G. TUCKER, M. D.

Director

RICHARD M. PEARCE, M. D.

Staff

(For the Year ending August 31, 1907.)

HOLMES C. JACKSON, Ph. D., *Physiological Chemistry*
LEON K. BALDAUF, M. D., *Pathology*
(Resigned May 31, 1907.)
LA SALLE ARCHAMBAULT, M. D., *Neuro-pathology*
FRANK GEORGE SCHAIBLE, M. D., *Bacteriology*
(Resigned June 30, 1907.)
J. FLETCHER ROBINSON, M. D., *Surgical Pathology*
(Resigned June 30, 1907.)
H. P. SAWYER, M. D., *Pathology*
(Appointed July 1, 1907.)
C. W. LOUIS HACKER, M. D., *Surgical Pathology*
(Appointed July 1, 1907.)
C. B. HAWN, M. D., *Bacteriology*
(Appointed July 1, 1907.)
T. F. DOESCHER, M. D. *Surgical Pathology*
(Appointed July 1, 1907.)

Pathological House-Officer

(Appointed by the Governors of the Albany Hospital.)

C. W. LOUIS HACKER, M. D.
(Resigned June 30, 1907.)
WM. A. KRIEGER, M. D.
(Appointed July 1, 1907.)

Assistant Chemist and Bacteriologist

(In charge of the Albany Filtration Plant.)

GEORGE E. WILLCOMB, S. B.

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Laboratory Courses of the Albany Medical College

(Given in the Bender Laboratory.)

Session of 1906–'07

Pathology and Bacteriology

RICHARD M. PEARCE, M. D., *Professor of Pathology and Bacteriology*

LEON K. BALDAUF, M. D., *Instructor in Pathology and Bacteriology*

FRANK GEORGE SCHAIBLE, M. D., *Instructor in Pathology and Bacteriology*

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Histology

GEORGE E. BEILBY, M. D., *Instructor in Histology*

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EDWIN F. SIBLEY, M. D., *Instructor in Surgical Pathology*

Clinical Microscopy

ARTHUR T. LAIRD, M. D., *Lecturer on Clinical Miscroscopy*

HARRY RULISON, M. D., *Instructor in Clinical Microscopy*

Anatomy and Pathology of the Nervous System

LA SALLE ARCHAMBAULT, M. D., *Instructor in Neurology*

Anatomy and Pathology of Obstetrics

H. JUDSON LIPES, M. D., *Clinical Professor of Obstetrics*

MALCOLM DOUGLAS, M. D., *Voluntary Assistant*

Experimental Physiology (2d year)

HOLMES C. JACKSON, Ph. D., *Adjunct Professor of Physiological Chemistry and Experimental Physiology*

J. F. ROONEY, M. D., *Instructor in Physiological Chemistry and Experimental Physiology*

Demonstrations in Physiology (1st year)

EDWARD W. BECKER, M. D., *Instructor in Physiology.*

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Original Communications

EXPERIMENTAL LIVER NECROSIS; I. THE HEXON BASES.[1]

By HOLMES C. JACKSON, Ph.D.,
Adjunct Professor of Physiological Chemistry,
AND
RICHARD M. PEARCE, M.D.,
Professor of Pathology and Bacteriology, Albany Medical College.

This communication is the first of a series of five, which presents the results of a somewhat comprehensive investigation of the chemical changes associated with experimental liver necrosis and which includes, in addition to that here presented, studies of the nitrogenous metabolism, nuclein metabolism, the activity of the intracellular hepatic enzymes and the changes in the fats and lipoids of the liver.

The advantage of undertaking such a comprehensive study was suggested by the investigations[2] which one of us had previously made of the necrosis caused in the liver of the dog by the intravenous or intraperitoneal injection of hemagglutinative and hemolytic immune sera. The lesions so produced are frequently focal and resemble in a general way those of eclampsia while the diffuse lesions, with the associated repair, are more or less similar to certain stages of acute yellow atrophy. It seemed plausible therefore that a study of the chemistry of such lesions, readily produced experimentally, might throw light not only on certain functions of the liver but might offer new knowledge of value in explaining some of the problems of eclampsia, acute yellow atrophy and similar lesions in man.

The study of the hexon bases was undertaken in the hope of determining the character of the processes underlying the production of *intra vitam* autolysis. We have therefore attempted to determine the relative enzymotic power of the normal and the necrotic liver in regard to the synthesis or

[1] Conducted under grants from the Rockefeller Institute for Medical Research. Read by title before the Society of Experimental Biology and Medicine, New York, March 20, 1907. Published also in *Journal of Experimental Medicine*, 1907, ix, 520.

[2] Pearce, R. M., The Experimental Production of Liver Necroses by the Intravenous Injection of Hæmagglutinins, *Jour. of Med. Research*, 1904, xii, 329; 1906, xiv, 541. Experimental Cirrhosis of the Liver, *Jour. of Exper. Med.*, 1906, viii, 64.

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decomposition of the hexon bases. The importance of these bodies, as products of autolysis, has been emphasized by Wakeman[3] in his study of the livers of dogs poisoned with phosphorus or repeatedly anesthetized with chloroform. In addition to the study of fresh tissues, we have investigated also the changes occurring in hexon nitrogen during antiseptic autolysis of liver substance.

The experimental lesions under consideration may be described, without going into detail, as hyaline necroses with little or no leucocytic reaction, the position and extent of which vary according to the amount of serum administered and the resistance of the animal. Small doses causes focal lesions more or less isolated and irregularly distributed; large doses produce a diffuse necrosis which spares only the tissue about the larger portal spaces. The lesions are found chiefly near the surface of the liver, but may occur in the deeper portions. In animals dying within a few hours after injection and before the appearance of necrosis an intense congestion of the entire portal system exists with, in the liver, innumerable thrombi composed of fused red cells.

In addition to such material from the dog, the livers of horses presenting degenerative and necrotic lesions, occurring in the course of immunization with various bacterial products, have also been utilized. These lesions, which have been described fully elsewhere by Pease and Pearce[4] and more recently by Lewis,[5] consist of widespread necrosis associated not infrequently with an extensive deposition of amyloid and usually accompanied by hemorrhages.

A series of fifteen livers, eleven from the dog and four from the horse, has been examined. Of the former, five were normal, four showed focal necroses and two diffuse necrosis; of the latter two were normal and two were examples of necrosis associated with extensive amyloid transformation.

Methods.—As a necrotic lesion in the dog's liver reaches its greatest extent in twenty-four to forty-eight hours after injec-

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[3] Wakeman, A. J., On the Hexon Bases of Liver Tissue under Normal and Certain Pathological Conditions, *Jour. of Exper. Med.*, 1905, vii, 292.

[4] Pease, H. D., and Pearce, R. M., Liver Necrosis and Venous Thrombosis in Horses Actively Immunized with Diphtheria and Tetanus Toxins and with Streptococci and their Products, *Journ. of Infect. Diseases*, 1906, iii, 619.

[5] Lewis, P. A., Hæmorrhagic Hepatitis in Antitoxin Horses, *Jour. of Med. Research*, 1906, xv, 449.

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tion, all livers used in the study of the hexon bases were taken from animals killed at the end of the latter period. In the case of the horses the livers were removed within one hour after death.

After cutting away the larger vessels and the coarser tissue about the hilum the organ was subdivided and passed through the hashing machine. Small portions were weighed and set aside for drying and upon these total nitrogen estimations were made later. At the same time two portions of 100 grams each of moist liver were placed in flasks. To one, 600 cubic centimeters of water and 300 grams of sulphuric acid were added and hydrolysis carried on for fourteen hours in a paraffin bath. The other sample was suspended in 600 cubic centimeters of water and with it were thoroughly mixed about fifty cubic centimeters of toluol. This flask plugged with cotton was allowed to stand at room temperature for periods of one or two months. At the end of this time it was examined bacteriologically, and if found free of bacteria, 300 grams of sulphuric acid were added and the material hydrolyzed in the same manner as the control. Subsequent treatment was carried out according to the method outlined by Wakeman except that the process was continued only to the point of making nitrogen determinations of fractions "A" (arginin and histidin) and "B" (lysin) after removal of the barium and silver by means of sulphuric acid and hydrogen sulphide. For our purpose no advantage was to be gained by separating arginin and histidin.

Dry Solid Content.—An examination of the figures in the table indicates that the dry solid content of the dog livers with scattered focal necroses did not vary from the normal average of 24 per cent. In the case of the diffuse lesions, where the autolysis of the protoplasm was obviously more marked, the dry solids were reduced to an average of 20.8 per cent. The figures referring to normal livers agree somewhat closely with those of Wakeman, who, however, noticed a slight decrease in the percentage of dry substance in the livers of dogs poisoned by phosphorus. This is somewhat surprising since he describes these livers as markedly fatty. If the protoplasm of which seventy-five per cent. is water is replaced by fat, which contains none, the dry solids should increase instead of decrease. If Wakeman's figures are correct they show a

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TABLE—*Hexon Bases.*

Nature of Experiment.		Determination on Fresh Tissue.						On Autolysed Tissue.			
		per cent.			*per cent. nitrogen.			Per Cent. of N_2 ppt. by Phosphotung. Acid.	*per cent nitrogen as		
Dog.	Condition of Liver	Dry Substance.	Nitrogen in Dry Substance.	N_2 ppt. by Phosphotung. Acid.	Arginin and Histidin.	Lysin.	Purin. Bases.		Arginin and Histidin.	Lysin.	Purin Bases.
3	Normal	24.8	12.1	13.2	4.3 / 32.5	3.6 / 27.1	5.3 / 40.4	Not bacteria-free			
4	Normal	18.4	10.9	15.0	6.0 / 40.0	4.9 / 32.7	4.1 / 27.3	19.8	8.4 / 42.4	9.8 / 49.5	1.6 / 8.1
13	Normal	26.8	11.8	Used only for autolysis				18.3	8.0 / 43.7	7.3 / 39.9	3.0 / 16.4
14	Normal	24.5	9.2	Used only for autolysis				17.6	7.5 / 42.6	7.6 / 48.2	2.5 / 14.2
17	Normal	25.0	11.2	19.6	4.3 / 36.2	7.4 / 37.7	5.1 / 26.1	20.4	8.0 / 39.2	7.9 / 38.7	4.5 / 22.1
Av.		23.9	11.3	15.9	6.0 / 36.2	5.3 / 32.5	4.8 / 31.3	19.0	8.0 / 42.0	8.2 / 42.8	2.9 / 15.2
5	Few focal necroses	24.4	21.4	12.2	5.6 / 45.8	4.2 / 34.4	2.4 / 19.8	9.0	4.1 / 45.5	2.7 / 30.0	2.0 / 24.5
7	Few focal necroses	16.6	19.1	14.5	7.3 / 50.2	5.1 / 35.1	2.1 / 14.7	10.2	4.9 / 48.0	3.5 / 34.3	1.9 / 17.7
9	Numerous focal necroses	26.9	22.8	10.2	4.8 / 47.2	3.2 / 31.5	2.1 / 21.3	6.7	2.3 / 34.3	2.6 / 38.8	1.8 / 26.9
10	Numerous focal necroses	25.6	23.7	8.5	3.6 / 42.3	2.5 / 29.4	2.4 / 28.3	6.8	2.7 / 39.8	1.9 / 27.9	2.1 / 32.3
Av.		23.4	21.8	11.4	5.3 / 46.4	3.8 / 32.6	2.2 / 21.0	8.2	3.5 / 41.9	2.7 / 32.8	2.0 / 25.3
29	Extensive diffuse necrosis	21.9	12.7	30.0	15.6 / 52.0	11.6 / 38.6	2.8 / 9.4	23.9	11.5 / 48.1	10.2 / 42.7	2.2 / 9.2
60	Extensive diffuse necrosis	19.8	13.2	25.6	12.7 / 49.6	11.3 / 44.1	1.6 / 5.3	20.7	10.1 / 48.8	9.5 / 45.9	1.1 / 5.3
Av.		20.8	12.95	27.8	14.2 / 50.8	11.5 / 41.4	2.2 / 7.4	22.3	10.8 / 48.5	9.9 / 44.3	1.7 / 7.3

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TABLE—*Hexon Bases (Continued)*.

Nature of Experiment.		Determination on Fresh Tissue.					
		per cent.			*per cent. nitrogen as		
Horse.	Condition of Liver.	Dry Substance.	Nitrogen in Dry Substance.	N_2 ppt. by Phosphotungstic Acid.	Arginin and Histidin	Lysin.	Purin Bases
60	Normal	23.3	12.0	8.1	3.0 / 37.0	4.6 / 56.7	0.5 / 6.3
65	Normal	21.8	11.2	8.5	3.9 / 45.9	3.1 / 36.5	1.0 / 17.6
Av.		22.6	11.6	8.3	3.5 / 41.5	3.9 / 46.6	0.75 / 12.0
42	Necrosis and amyloid	20.0	21.7	13.5	2.9 / 21.4	8.2 / 60.7	2.4 / 17.9
69	Necrosis and amyloid	21.4	13.7	13.3	1.2 / 9.0	10.2 / 76.7	1.9 / 14.3
Av.		20.7	17.7	13.4	2.1 / 15.2	9.2 / 68.7	1.9 / 16.1

*Figures in upper left hand corner are calculated on the total nitrogen; those in the lower right hand corner on the total hexon nitrogen.

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marked increase in the water content of the organs during phosphorus poisoning. That such an increase may occur did not appear in our investigation[6] of fatty changes in the liver.

Total Nitrogen Content.—Several interesting facts developed from the analysis of the nitrogen of the dry solids. The average of the five determinations for normal tissue was 11.3 per cent. in agreement with Wakeman; while that of the livers with lesions of a scattered focal character was 21.8 per cent.

This, of course, indicates a deposition or heaping-up of nitrogenous material in the hepatic cell. That such a process may take place even under physiological conditions is evident from the results of experiments carried out by Seitz.[7] This investigator found that by feeding hens and geese excessive amounts of meat a true deposition of nitrogenous substances occurred in the cells of the liver. This increase amounted in some instances to 300 per cent.

In our experiments the quantity of nitrogen in the hepatic cell was almost doubled in the organs with scattered necrotic lesions. This condition allows of an explanation similar to that offered for the infiltration of fat in tissues during phosphorus or phloridzin poisoning. In such lesions the cells have lost in part their power to oxidize properly the sugar or other materials placed at their disposal by the circulating blood and hence the starving cell, in its endeavor to spare its own protoplasm from destruction, stores up fat for purposes of oxidization.

That the cells at the margin of the necroses under consideration do accumulate fat we have observed in our study of the histological changes occurring in these livers.[6] It seems distinctly possible that during the initial stage of congestion and thrombosis and in the early stages of necrosis, the imperfectly nourished and slightly injured cells may heap up nitrogenous material also. When, however, the lesion is more extensive, the storing up of nitrogen is not so evident as shown by the fact that the nitrogen of the dry solids remains more nearly normal. This is to be explained by assuming that the nitrogen stored up in the persisting liver cells is

[6] See fifth paper of this series, "The Fats and Lipoids."

[7] Seitz, W., Die Leber als Vorrathskammer für Eiweissstoffe, *Arch. f. ges. Physiol.*, 1906, cxi, 309.

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sufficient to more than balance the loss by autolysis in the necrotic areas.

Wakeman's figures for the nitrogen content of livers after phosphorus poisoning show a diminution equivalent to 35.6 per cent. and a corresponding decrease in the hexon base nitrogen. This indicates, according to his view, that that part of the proteid molecule involving the hexon bases has not undergone a relatively greater decomposition than the other nitrogenous substances. It would seem to us that the low nitrogen content of the phosphorus livers is wholly, or in greatest part, due to the large amount of fat present.

The Hexon Bases.—Wakeman's results indicate that in the dog the average nitrogen content of the bases in the normal liver tissue is 17.04 per cent. of the total nitrogen, while in the liver of dogs poisoned with phosphorus it is only 10.72, a falling off of 37.1 per cent. The livers of dogs receiving chloroform showed 13.6 per cent., a decrease of 20 per cent. In these figures Wakeman sees evidence of increased autolysis in hepatic cells affected by phosphorus or chloroform. Although he mentions definite necrosis in but one of his livers, the cell destruction in phosphorus poisoning, gradual as it is, is such that our results ought to fall, as they do, somewhat into line with his.

Thus as an average of three normal livers we find the figures concerning the total content of hexon bases, based on nitrogen content attributable to them, to be 15.9 per cent. of the total nitrogen. In the case of the scattered focal necrosis, the percentage is slightly decreased to 11.4 as an average of four determinations, but the absolute amount is increased. That is gram for gram of dry substance there occurs an increase in the absolute amount of hexon bases which however appears as a decrease in percentage on account of the high nitrogen content of the dry substance.

This absolute increase in hexon content of dry substance is greater and more clearly accentuated in the livers of those dogs in which the necrosis is more diffuse. Here the nitrogen of the dry substance is almost the same as that of the normal, 12.95 per cent. as average of two determinations; but the hexon base nitrogen content rises to 27.8 per cent. of the nitrogen of the dry substance.

This observation is extremely interesting in that it points most

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strongly to the preponderance of the autolytic process over the synthetic in the more widespread forms of necrosis with early repair. The figures show a definite increase in the hexon base content of the necrotic cell, although the accumulation of nitrogen in this lesion, 12.95 per cent., could not occur to such a marked extent as it did in the local lesion, 21.8 per cent., because of the lessened number of persisting living cells capable of storing up nitrogen. A rearrangement of nitrogen, the result of autolysis in the larger areas of necrosis, therefore took place as shown by the hexon nitrogen content of 27.8 per cent., as compared with that of 11.44 per cent. in the focal lesion and 15.9 per cent. in the normal. This great increase of hexon bases may be due in part also to disturbances of the circulation accompanying the necrosis which prevent the diffusion and removal of the bases from the liver. In this connection attention may be called to Jacoby's[8] observations that leucin and tyrosin are not found in the liver of phosphorus poisoning when no disturbance of the hepatic circulation exists.

Relation of Precipitate "A" (Arginin and Histidin) and Precipitate "B" (Lysin) to the Total Hexons.—Wakeman, from a consideration of his results on these fractions, concludes that in the autolysis which occurs in the cell in phosphorus poisoning the arginin suffers a greater destruction than do the other bases, probably through the action of arginase, which splits arginin into ornithin and urea.[9] His tables show that of the 17.0 per cent. of the nitrogen of the total bases in the normal tissues, 11.8 per cent. is to be attributed to arginin and histidin and 5.2 to lysin. In phosphorus poisoning, on the other hand, the nitrogen of the bases amounts to 10.7 per cent., of which only 6.8 per cent. belongs to the arginin and histidin and 3.8 per cent. to the lysin. This indicates a decrease during autolysis of 42.3 per cent. for the arginin and histidin, but only 26.8 per cent. for the lysin.

If, however, one considers these figures from the standpoint of the relationship which the precipitates "A" and "B" bear to the total hexon bases of the normal and phosphorus dogs, an entirely different view is obtained. In the normal tissue

[8] Jacoby, M., Ueber die Beziehungen der Leber und Blutveränderungen bei Phosphorvergiftung zur Autolyse, *Zeit. f. physiol. Chem.*, 1900, xxx, 174.

[9] Kossel, A., and Dakin, H. D., Ueber die Arginase, *Zeit. f. physicol. Chem.*, 1904, xli, 321.

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precipitate "A" (arginin and histidin) forms 69.6 per cent. and precipitate "B" (lysin) 30.4 per cent. of the total bases; whereas in the phosphorus livers the former is 63.9 per cent. and the latter 36.1 per cent. Hence the decrease in the fraction "A" is only 5.7 per cent. and this is offset by the corresponding increase in fraction "B." This diminution in the arginin and histidin content of the hexon base fraction of the livers of phosphorus-poisoned animals compared with the normal is so slight that it hardly seems warrantable to attribute it to the action of arginase.

Our figures for the total hexon bases (15.9 per cent.) in the normal agree well with those found by Wakeman while those for the focal necroses have suffered a percentage decrease which is somewhat comparable to that noticed by him in phosphorus poisoning. Wakeman's percentage decrease, however, was also an absolute one while ours in reality was an absolute increase, as has been explained above. The proportion which precipitates "A" and "B" bear to the total is markedly different, however, from that which he notes. Our average in the normal tissues for the arginin and histidin fraction is 36.2 per cent. as against 69.4; the lysin fraction 32.5 per cent. more nearly agrees with his 30.3 per cent. If we exclude the purin bases our results become more comparable and agree better in percentage.

We have also found a much greater percentage of the total nitrogen due to purin bases. Wakeman's figures show an average of 0.0273 per cent. for normal and pathological, while ours showed 4.8 per cent. for the normal tissue against 2.2 per cent. for the focal necrotic lesions and the same for the diffuse necrosis.

As to variations which the individual bases undergo in their relation to the total bases, our results point to an increase from the normal of 36.2 per cent. to 46.4 during the focal necrosis and to 50.8 per cent. during diffuse necrosis for arginin and histidin. The lysin fraction shows no change in the focal necroses as compared with the normal, but in the diffuse necrosis it increased 24.3 per cent over the normal in agreement with Wakeman.

In the autolysis *in vitro*, which is discussed in the next paragraph, the normal fraction "A" represented 42.0 per cent. of the whole bases and fraction "B" 42.8 per cent.—differ-

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ences from the normal which are well within the limit of error. Hence the absolute increase from 6.0 and 5.3 in the unautolyzed to 8.0 and 8.2 per cent. of the total nitrogen in the tissue after autolysis was in exact relation to the increase in total hexon nitrogen. The same is true for the autolyzed tissue with necrosis of all types.

This would emphasize more markedly the point made above that small evidence can be adduced to show that an enzyme, arginase, is acting on the arginin, decreasing its amount during autolysis. Such action is not shown by our figures and moreover in our investigation of intracellular hepatic enzymes[10] we could not obtain an active arginase from the necrotic dog's liver, though it was found in the normal.

Hexons Resulting from Autolysis in Vitro.—It seemed worth while in view of the investigation, carried on synchronously, of intracellular hepatic enzymes[10] to determine the relation of the hexon bases to autolysis of the liver *in vitro*. For such observations the figures given above for autolysis during life serve as controls. Autolysis was allowed to proceed for varying lengths of time in the endeavor to determine whether the different organs showed varied degrees of autolysis. The periods selected, one and two months, were inadequate to bring out this point, since the autolysis was completed or the reaction reached its equilibrium before one month. This was unfortunate as we thereby disregarded the important element, that of time, in this connection. The time element, however, is fully considered elsewhere[10] from another point of view.

A glance at the figures in the table shows that after autolysis of the normal organs the percentage of total nitrogen as hexon nitrogen was 19.0 per cent. as an average of four determinations. This increase of 18.8 per cent. over the normal hexon content is not marked, and if one examines the figures referring to the two dogs (4 and 17) upon which alone we have absolute controls, it will be seen that this increase is variable.

We are not inclined to attempt to explain this result in detail in this place, since the data which we will present in our study of the enzymes bear more decisively upon this matter. Suffice it to say that these figures, taken in connection with

[10] See second paper of this series, "Enzymes."

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those of the diffusely necrotic organs where an increase also was evident, indicate that in the autolysis a transformation or rearrangement occurs by which nitrogenous atomic complexes, not normally yielding hexon bases, become altered into hexon bases or their combinations.

In all degrees of necrosis, the autolyzed material contained a smaller amount of hexon bases than the unautolyzed. In the liver with scattered focal necroses the decrease of the hexon nitrogen in per cent. of the total nitrogen amounted to 28.0 per cent.; in the diffuse necrosis 19.8 per cent. This would seem to imply that in the living tissue the hexon splitting enzyme is to some degree inhibited, probably through the action of the blood serum.

Hexon Bases in the Liver of the Horse.—The results obtained with the normal livers of horses agree in regard to the dry solids (22.6 per cent.) and the nitrogen of the dry tissue (11.6 per cent.) with those obtained for the dog. The nitrogen precipitable with phosphotungstic acid, however, is surprisingly low, amounting to only 8.3 per cent. It would seem inadvisable to attempt an explanation of this difference, since these animals were not absolutely normal, in that they had been utilized for the purpose of preparing antitoxin and had died during such treatment, though no lesions were found in the liver. The injection of bacterial products may set up processes in the cell which tend to reduce its hexon content without changes evident histologically. The percentage which fractions "A" and "B" of such livers bears to the total hexon content is not far removed from that found for each in the case of the normal dog liver.

The two lesions which served as examples of necrosis presented the complicating feature of amyloid. This fact renders the series not exactly comparable to the previous one. The increase in nitrogen of the dry substance over that of the normal is present here also, and the total hexon base nitrogen has increased to 13.4 per cent. This latter result may be caused by the heaping up of the bases as products of autolysis in the large necrotic areas. More probably, however, it is to be attributed to the amyloid degeneration, in which the normal cellular proteids with relatively small percentage (10-30 per cent.) of diamino-nitrogen are replaced by amyloid, the proteid constituent of which, in the liver and spleen as

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shown by Neuberg,[11] contains twice as much (50-60 per cent.) diamino-acid nitrogen. This rearrangement in the hexon content of the proteids of the organ has also resulted in a marked change in the relation which the arginin and histidin as well as the lysin bears to the total amount of hexon base precipitate. "A" forms only 15.2 per cent. and precipitate "B" 68.7 per cent. of the whole diamino-acid nitrogen.

SUMMARY.

1. The liver of the dog in which necrosis has been produced by injection of hemotoxic immune sera is characterized in the less marked forms by a storing up of nitrogen in the persisting living cells, while in the diffuse forms the total nitrogen content is but slightly above the normal. This last is to be explained by the great diminution in persisting liver substance which limits the power of nitrogen accumulation.

2. In all forms of necrosis there occurs an absolute increase of nitrogen precipitable by phosphotungstic acid (hexon bases) but the percentage increase, in relation to total nitrogen, diminishes in those forms (focal) in which the products of autolysis may be readily carried off by the blood stream and greatly increases in the diffuse form with large areas in which the circulation is seriously impaired.

3. Although the absolute amount of nitrogen representing arginin and histidin varies, a relative increase is evident when this fraction is compared with the total diamino-nitrogen. This increase corresponds to the degree of necrosis and attendant circulatory disturbance and indicates that in necrosis as opposed to degeneration (Wakeman) arginin is not split up by arginase. The lysin also bears a definite relation to the total hexon nitrogen.

4. The diamino-nitrogen of the normal liver after autolysis *in vitro* shows a slight variable increase over that of the unautolyzed, while the necrotic livers showed a decided decrease.

5. The diamino-acid nitrogen of normal horse liver is only about one-half of that of the dog; the relative proportion of the bases is about the same. In necrotic livers with amyloid the diamino-nitrogen is markedly increased which is in accord with Neuberg's observations on the high hexon base content of amyloid.

[11] Neuberg, Ueber Amyloid, *Verhand. d. Deut. path. Gesellsch.*, 1904, vii, 19.

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Conclusions.—Upon the whole then the chemical processes occurring in the hepatic cell undergoing rapid or immediate necrosis and those accompanying a slow "degeneration," as for example in phosphorus poisoning, must be different and distinct as would be expected from the histological findings. In necrosis we find the cell in a complete state of disorganization and decomposition and hence autolysis begins immediately, but in the changes occurring in the cell in the so-called degenerations, as phosphorus poisoning, the nucleus remains intact, thereby insuring to a certain extent the life or at least partial function of the cell. That under the latter circumstance a disturbed condition does exist is evidenced by the heaping up of fat in the cell, and although the results of the various investigations upon the altered processes in the liver of animals poisoned with phosphorus tend to show that this change is an autolysis, in which certain amino-acids appear as the result of the splitting of the proteid molecule, it is not of the same type as that appearing in the necrotic cell. This is shown by a comparison of Wakeman's findings, which indicate definitely a diminution of hexons in the liver, with ours which show a great increase.

Examinations of the human liver, by a direct method without hydrolysis, but few in number, it is true, tend to the same conclusion. Taylor,[12] for example, found arginin in a liver with widespread necrosis, the result apparently of chloroform poisoning; from seven other livers, representing various lesions (dysenteric abscess, fatty degeneration, pyemia and acute yellow atrophy), he was unable to isolate this substance. Soetbeer[13] also was unable to find hexon bases in a peculiar type of cirrhosis with acute degeneration.

This difference in the hexon content of the liver of "degeneration" and that of necrosis is so striking that it would appear to be due to a difference in the nature or rapidity of the cell destruction, though it may to some extent be explained by the disturbances of circulation which occur in the necrosis and which, presumably, are absent in degeneration.

[12] Taylor, A. E., Ueber das Vorkommen von Spaltungsprodukten der Eiweisskörper in der degenerirten Leber, *Zeit. f. physiol. Chem.*, 1902, xxxiv, 580. On the Occurrence of Amino-acids in Degenerated Tissue, *Univ. of California Publications*, 1904, i (Path.), 43.

[13] Soetbeer, F., Ueber einen Fall von akuten Degeneration des Leberparenchyms, *Arch. f. exper. Path. u. Pharm.*, 1903, l, 294.

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Our observations show also that care must be exercised in drawing conclusions from results obtained by autolysis *in vitro*. It seems distinctly doubtful whether the autolysis of the cell which occurs under such circumstances has any relation to autolytic changes during life.

EXPERIMENTAL LIVER NECROSIS; II. ENZYMES.[1]

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The experiments about to be described represent an attempt to determine the relation of the intracellular hepatic enzymes to chemical changes occurring in liver necrosis. Our results are based on a comparison of the variations in the enzymotic equilibrium of the normal hepatic cells with those occurring in necrosis of varying grades of severity. At present the chief and most promising method of detecting such variations consists in determining by means of post-mortem autolysis the condition under which the cell is existing at the time of the death of the animal, and the rapidity, nature and extent of the changes which occur after the commencement of the autolysis. We are well aware that the interpretation of the results of post-mortem autolysis in relation to cellular activity during life is open to objection and may not have the importance usually ascribed to it.

Our investigation of the enzymotic activity of the liver tissue under normal circumstances and in varying degrees of necrosis may naturally be subdivided as follows:

1. A determination in a quantitative way of the degree of autolysis which the tissue undergoes after death.

2. A study of the individual enzymes with reference to the part which they play in the general course of autolysis.

3. A determination of the products formed as the result of

[1] Conducted under grants from the Rockefeller Institute for Medical Research. Read by title before the Association of American Physicians, Washington, May 9, 1907. Published also in *Journal of Experimental Medicine*, 1907, ix, 534.

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such autolysis. These include the diamino-acids, which have been considered in the preceding paper,[2] where they more properly belong, and the monamino-acids to which, as represented by leucin and tyrosin, we have given considerable attention. It was our intention to determine, by perfusion of livers in various stages of necrosis, the changes in the composition of the blood which might occur, but owing to the great amount of labor entailed in the present studies this has been unavoidably postponed.

Comparative Estimation of Products of Autolysis.—In the study of the changes which the nitrogenous material undergoes during autolysis *in vitro* an attempt was made to carry out a partition analysis of the non-coagulable nitrogen. This method has already been employed with good results by v. Drjewezki[3] to determine the effect of alkalies of varying strengths upon autolysis. His results, as well as those of Wiener,[4] point to the sensitiveness of the autolytic enzymes to changes in reaction, especially those due to alkalies, and these investigators conclude that the alkalies of the serum are responsible for the well-known inhibitory effect of the serum upon autolysis. Baer[5] and his associate, Loeb,[6] admit the inhibitory effect of the serum but are inclined to attribute it to the action of the serum globulin.

These facts, as well as those brought out by Lang,[7] concerning the inhibitory effect of large quantities of toluol upon autolytic processes, although other factors may have influenced the results of the latter, all tend to emphasize the fact that in performing experiments of this character too much attention cannot be given to the attainment of absolutely comparable conditions in all the various experiments. With these points in mind we have endeavored to control our work in every way, as is shown in the following detail of the experiments.

Quantities of the fresh tissue of known weight were ground to such a state of subdivision that when mixed with water or neutral

[2] See first paper of this series, "Hexon Bases."

[3] v. Drjewezki, A., Ueber den Einfluss der alkalischen Reaktion auf die autolytischen Vorgänge in der Leber, *Biochem. Zeit.*, 1906, i, 229.

[4] Wiener, H., Ueber den Einfluss der Reaktion auf autolytische Vorgänge, *Zent. f. Physiol.*, 1905, xix, 349.

[5] Baer, J., Ueber die Wirkung des Serums auf die intracellularen Ferments, *Arch. f. exper. Path. u. Pharm.*, 1906, lvi, 68.

[6] Baer, J. and Loeb, A., Ueber die Bedingungen der autolytischen Eiweissspaltung in der Leber, *Arch. f. exper. Path. u. Pharm.*, 1905, liii, 1.

[7] Lang, S., Ueber desamidierung im Tierkörper, *Beit. z. chem. Physiol. u. Path.*, 1904, v, 321.

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Ringer's solution the mixture could be readily drawn up in a pipette. This mixture, usually consisting of two hundred grams of liver, was made up to 1,200 cubic centimeters and placed in a sterile flask and the mixture covered with a layer of toluol. This latter substance was well shaken in, after which were pipetted off, as controls, two samples of two hundred cubic centimeters each. Both were thoroughly sterilized in the autoclave in order to stop autolysis; one was examined immediately, as an initial control, the other was placed with the original mixture in the thermostat (37.5° C.) and examined at the conclusion of the experiment as a final control. The material in the thermostat was shaken from time to time and at intervals of one, three, five and eight days samples of the main mixture were removed for analysis by the same method as the controls. The analysis of the samples, after they were shown to be bacteria free,[8] took place in the following manner:

The mixture was pipetted into a beaker and sufficient water was added to allow of easy coagulation of the proteid material present. Acetic acid was added to slightly acid reaction after the boiling point was reached. The coagulated proteid was removed by filtration and repeatedly and thoroughly washed with boiling water. The volume of the filtrate and washings was made up to eight hundred cubic centimeters. Of this, twenty-five cubic centimeters served for the determination of the total nitrogen by the Kjeldahl-Gunning method, one hundred for the estimation of ammonia according to the method of Shaffer as applied to the urine, one hundred for the uric acid determination, using the Hopkins-Folin method, and fifty to determine the amount of nitrogen not precipitable by phosphotungstic acid in sulphuric acid solution, the so-called monamino-nitrogen. An attempt was also made to determine the nitrogen precipitable (proteoses) by zinc sulphate but our results are so incomplete that little can be gained from their discussion. In all cases duplicate determinations were made and the figures given represent their average. Dogs were employed in all experiments.

In Table I are presented the results of the nine experiments which differed in their conditions for the purposes of control, as follows:

Two normal livers (52 and 54) with their usual blood content, the diluting fluid of one being distilled water and of the other neutral Ringer's

[8] For this purpose it was deemed sufficient merely to examine stained films though when the final sample of each mixture was taken cultures were made. In this series representing nine livers no contamination occurred.

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solution. This solution was prepared in the ordinary way with the exception that the sodium bicarbonate was not added in order to avoid an alkaline medium.

Two normal livers (53 and 58) washed *in situ*, the one with water and the other with neutral Ringer's solution.

One necrotic liver four hours after injection (57). An attempt was made to wash this liver with water but on account of the extensive thrombosis it was only partly successful. It is therefore referred to as "halfwashed."

Two necrotic livers forty-eight hours after injection (48 and 56); one unwashed diluted with water; the other washed and diluted with neutral Ringer's solution.

Two livers (43 and 49) five days after injection, both showing necrotic lesions with early repair; one washed and diluted with Ringer's, the other unwashed but diluted with water.

In each instance in which the livers were washed the procedure was begun under ether while the animal was alive. With the exception noted the livers were completely blanched save for slightly tinged areas about the more diffuse foci of necrosis.

The results in Table I, in terms of nitrogen, are expressed in percentages of the total nitrogen of the dry tissue and of the total non-coagulable nitrogen. A critical consideration of the figures presented allows of the following statements:

Non-coagulable Nitrogen.—The inhibiting effect of the blood serum upon the extent of the autolysis of both normal and necrotic tissue is decisively shown. The percentage of non-coagulable nitrogen in the case of the unwashed normal organs increased from 10.7 and 9.7 to 19.9 and 29.1 per cent. respectively, an increase of 100 and 200 per cent., on the eighth day; while in the washed normal livers the average increase at the eighth day amounted to 450 per cent. The increase in the five day necrotic unwashed liver was 127 per cent.; that of the washed tissue 349 per cent. The forty-eight hour washed tissue (Dog 56) with a very extensive necrosis, showed the greatest increase, equivalent to 856 per cent. of the control. The increase of the four hour experiment (congestion and thrombosis) hardly equaled that of the washed normal.

Wherever water was employed in washing or in diluting, the autolysis was distinctly less than when neutral Ringer was used. (Compare Dogs 52 and 54.)

Concerning the rapidity of the autolysis, it may be noticed that, though the initial increase during the first day in the case of the unwashed tissues is but one-half of that of the washed,

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TABLE I.—*Autolysis; nitrogen partition.*

NORMAL.				4 HOURS.	48 HOURS.	NECROSIS.	5 DAYS.	NECROSIS.	DURATION.
Not Washed.		Washed.		Washed.*	Not Washed.	Washed.	Not Washed.	Washed.	
52†	54	53	58	57	48†	56	43†	49	
Percentage of total nitrogen in non-coagulable form.									
10.7	9.7	13.5	9.5	8.5	12.7	8.3	26.6	18.3	Control
15.5	18.6	35.5	23.6	19.3	20.0	18.5	39.4	41.1	1 day
18.2	27.8	57.6	38.5	24.1	24.9	65.1	51.1	48.5	3 days
19.8	27.8	67.5	49.7	29.6	30.8	75.7	54.3	61.0	5 days
19.9	29.1	70.1	54.2	37.9	32.1	79.4	60.4	82.3	8 days
13.4	11.6	14.0	8.9	7.4	14.5	7.2	22.1	18.1	Final Control
Phosphotungstate-filtrate nitrogen (monamino-acid).									
7.2 / 12.4 / 14.1 / 16.2 / 16.9 / 8.4	67.3 / 80.0 / 77.5 / 81.8 / 84.9 / 63.0	7.4 / 30.9 / 49.8 / 56.9 / 57.8 / 7.6	54.8 / 87.0 / 86.6 / 84.3 / 80.1 / 54.1	4.2 / 18.2 / 31.8 / 40.3 / 46.2 / 4.8	44.5 / 77.1 / 82.6 / 81.0 / 85.2 / 54.3	5.5 / 14.7 / 19.9 / 25.3 / 32.3 / 6.8	64.7 / 72.8 / 82.5 / 85.4 / 85.2 / 90.5	10.7 / 17.2 / 22.6 / 26.0 / 27.2 / 8.9	81.1 / 86.0 / 90.8 / 84.4 / 84.7 / 75.4	3.6 / 16.4 / 54.7 / 64.3 / 70.1 / 3.7	43.0 / 88.6 / 84.2 / 84.9 / 88.3 / 52.5	15.0 / 29.7 / 37.2 / 43.8 / 46.9 / 11.9	56.5 / 75.4 / 72.8 / 80.7 / 77.6 / 53.8	11.3 / 30.0 / 39.3 / 53.0 / 71.9 / 11.9	51.7 / 73.1 / 81.0 / 86.9 / 87.3 / 66.0	Control / 1 day / 3 days / 5 days / 8 days / Final Control
6.7 / 13.7 / 21.4 / 22.9 / 23.9 / 8.1	69.3 / 73.6 / 77.0 / 82.4 / 82.7 / 70.0															
Ammonia nitrogen.																
0.74 / 1.38 / 1.45 / 1.63 / 2.08 / 0.66	6.9 / 8.8 / 7.9 / 8.2 / 10.4 / 4.9	0.59 / 1.41 / 2.45 / 2.52 / 2.45 / 0.67	4.3 / 4.0 / 4.2 / 3.8 / 3.5 / 5.2			0.79 / 1.05 / 1.9 / 1.6 / 2.9	9.4 / 5.4 / 7.9 / 5.4 / 7.6	0.80 / 1.46 / 2.16 / 2.19 / 2.34 / 1.02	6.3 / 7.3 / 8.6 / 7.1 / 7.3 / 8.6	0.85 / 1.50 / 2.78 / 3.25 / 3.01 / 0.85	10.2 / 8.1 / 4.3 / 4.3 / 3.8 / 11.6	2.08 / 4.4 / 4.7 / 5.8 / 6.4 / 2.2	8.6 / 10.6 / 9.2 / 9.6 / 10.6 / 10.0	1.10 / 2.20 / 3.30 / 3.99 / 5.11 / 1.43	6.0 / 5.3 / 6.9 / 6.5 / 6.2 / 7.9	Control / 1 day / 3 days / 5 days / 8 days / Final Control
0.49 / 0.90 / 1.06 / 1.60 / 1.22	5.1 / 4.8 / 3.8 / 5.1 / 4.2															

*Washing incomplete. †Distilled water used instead of neutral Ringer's solution.
Figures in upper left-hand corner show percentage of total nitrogen; those in lower right-hand corner, of non-coagulable nitrogen.

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it represents, as does also the increase of the washed, fifty per cent. of the total autolysis. On the third day, however, the autolysis has reached its maximum in the unwashed tissues, while the washed organs continue to increase until the eighth day, when the autolysis in their case is also apparently complete.

In the forty-eight hour lesions in which, histologically, the autolysis of the necrotic areas would appear to be at its height, we see that the autolytic processes *in vitro* were also very active. The increase at the end of the eighth day in the unwashed liver (Dog 48) was about 150 per cent., but after the removal of the inhibitory action of the blood (Dog 56) the increase rose to almost 900 per cent. The same thing is evident in the fifth day lesions but is not so pronounced.

The rapidity with which the autolysis reaches its maximum is of course dependent upon various factors. The attainment of the maximum signifies that the reaction velocities of the system, made up of substrat, hydrolytic agent and enzyme, have reached an equilibrium, caused, no doubt, by the non-removal of the products of autolysis. Since we must assume that the substrat and enzyme are the same in the normal tissues of both washed and unwashed organs, the varying factor must consist in the hydrolysis which, from the work of Wiener, seems undoubtedly due to the unneutralized acids formed during autolysis as first described by Magnus-Levy.[9] The acids which are formed in the normal metabolism of the cells are neutralized by the ammonia and excess of bases in the blood; hence autolysis does not occur in the living cell. As soon as the serum with its neutralizing power is removed, as in the washed organs or where the acids use up the excess of bases as in the center of a large area of necrosis, the conditions necessary for autolysis are present and hydrolysis of the substrat protoplasm takes place.

Phosphotungstate Filtrate Nitrogen (Monamino-acids).—The phosphotungstate precipitate has been disregarded here, for, as it consists of diamino-nitrogen it has been sufficiently covered in the autolysis experiments in connection with the study of the hexon bases.[10]

By far the major portion of the nitrogen in the filtrate is in

[9] Magnus-Levy, A., Ueber die Säurebildung bei der Autolyse der Leber, *Beit. z. Chem. Physiol. u. Path.*, 1902, ii, 261.

[10] See first paper of this series, "Hexon Bases."

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the form of monamino-acids.[11] The table indicates the percentage of the fraction in terms of the total nitrogen of the tissue as well as of the total non-coagulable nitrogen. Our figures for the controls indicate that in the normal tissue, washed or unwashed, 4.2 to 7.4 per cent. of the total nitrogen is to be attributed to nitrogen not precipitable with phosphotungstic acid. Of the forty-eight hour lesions, that with the most marked diffuse necrosis (Dog 48) showed 10.7 per cent. of the total nitrogen in that form, while the other, of the focal type (Dog 56), had only 3.6 per cent. or slightly less than the lowest of the normal figures. Also, in the first of this pair, 81.1 per cent. of the non-coagulable nitrogen was in the form of monamino-acid while the other showed only 43.0, again somewhat less than normal.

These two experiments illustrate most decisively the point which Taylor's[12] results seem to indicate. That is, there is an absence of monamino-acids in pathological conditions of the liver accompanied by little or no necrosis, while in necrosis of the diffuse type both the monamino- and diamino-acids are present. We have elsewhere[13] suggested that the relation of circulatory disturbances to the removal of the products of autolysis is an all-important factor. This is further supported by the two experiments under discussion which indicate that the organ with the focal lesions contained no more monamino-nitrogen than did the normal tissue. In this case the circulation was very slightly, if at all, impaired, and these acids, if they were formed, were removed immediately by the blood stream. In Experiment 48 the large necrotic areas, the centers of which were remote from circulatory fluids, held the acids as they were produced. That these substances are produced in autolysis of this type *in vivo* in large quantities is also indicated by the fact that 81.1 per cent. of the non-coagulable nitrogen of this liver was present in the fresh tissue as nitrogen non-precipitable with phosphotungstic acid. This value approaches that found in all the other cases after autolysis *in vitro* has proceeded for from one to three days.

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[11] v. Drjewezki, A., Ueber den Einfluss der alkalischen Reaktion auf die autolytischen Vorgänge in der Leber, *Biochem. Zeit.*, 1906, i, 229.

[12] Taylor, A. E., Ueber das Vorkommen von Spaltungsprodukten der Eiweisskorper in der degenerirten Leber, *Zeit. f. physiol. Chem.*, 1902, xxxiv, 580. On the Occurrence of Amino-acids in Degenerated Tissue, *Univ. of California Publications*, 1904, i (Path.), 43.

[13] See first paper of this series, "Hexon Bases."

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The control figures of the five day necrosis, as shown by Experiments 43 and 49, also indicate a high percentage of the total nitrogen of the tissue as monamino-nitrogen. As, however, an unusually large amount of the total nitrogen occurs in non-coagulable form the percentage relation of the monamino acids to the latter is about normal. These lesions were very extensive but of the focal type and the cells at the fifth day were undergoing repair. Hence, although autolytic processes were going on in the tissue at that time, the products were removed as fast as they were formed and no increase in amount occurred in the organ.

The same differences in the velocity and degree of autolysis *in vitro* between the washed and unwashed organs are also very evident and require no discussion since they are due to the same causes. It is interesting to note that the nitrogen occurring as monamino-acids reaches at the end of the first day about 80 per cent. of the non-coagulable nitrogen and then although autolysis may greatly increase, their formation increases only in the same proportion. The exception to this is in case of Dog 48, already discussed, where the percentage was high in the tissue itself and remained at the same level during autolysis *in vitro*. This would seem to point to the fact that as far as monamino-acids are concerned their formation in autolysis *intra vitam* occurs in the same manner and by the same chemical processes as they do in autolysis *in vitro*.

v. Drjewezki found that at the end of seventy-two hours autolysis the monamino-acids took up about sixty per cent. of the total nitrogen of the tissue. This figure is somewhat higher than we obtain at this stage of autolysis but in some instances it was reached on the fifth or eighth day.

Ammonia.—As a result of the work of Loewi,[14] Jacoby,[15] Lang and others, considerable interest has become attached to the power of the surviving liver tissue to produce ammonia, especially in view of the current opinion as to the importance of this product, after it has been split off from the amino-acids, as a step in the formation of urea. This interest has been heightened by the appearance of ammonia in increased absolute and percentage amounts in the urine in certain hepatic disorders, thus apparently bringing these matters into correlation.

[14] Loewi, O., Ueber das Harnstoffbildende Ferment der Leber, *Zeit. f. physiol. Chem.*, 1893, xxv, 511.

[15] Jacoby, M., Ueber die fermentative Eiweissspaltung und Ammoniakbildung in der Leber, *Zeit. f. physiol. Chem.*, 1900, xxx, 149.

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We have studied the question in two ways. First, in connection with the nitrogen partition of the autolysis now under discussion, and secondly, after the manner of the discoverer[15] of the ammonia-forming power of the liver. This latter part of the work will be discussed separately.

In the partition tables it is seen that although the ammonia content of the necrotic livers is greater than that of the normal it runs parallel with the increase in the amount of non-coagulable nitrogen, Hence the percentage figures show no regular increase or diminution though variations occur owing to the large limit of error dependent on the small amounts of ammonia formed. A comparison of a forty-eight hour necrotic liver (56), which offers an exception to the above statement, in that it shows a progressive diminution with a normal washed liver (53), is instructive. In 53 the normal percentage of ammonia of the non-coagulable nitrogen runs along about four per cent. throughout the experiment. In 56, however, the control shows a high initial ammonia content (10.2), which on the third day dropped to that of the normal washed liver (53) and remained at that level to the end of the experiment.

We explain this variation in the ammonia formation by the assumption that this tissue contained *intra vitam*, as the result of the necrosis, proportionately larger amounts of ammonia liberating compounds than the normal. As, however, the autolysis proceeded less of these products were formed in relation to the non-coagulable nitrogen than was the case in the autolysis of the normal. Hence the percentage figure dropped. Or if we allow for the initial difference we find that the percentage increase is the same in both cases.

The great increase in the amount of non-coagulable nitrogen which occurred between the first and third day (18.5 to 65.1 per cent.) in Dog 56 could not have included the formation of ammonia compounds, since the increase of these latter bodies in relation to the total nitrogen was so slight that there occurred an actual percentage decrease in relation to the non-coagulable nitrogen.

All this would seem to indicate that the production of ammonia which occurs in the autolysis of the liver *in vitro* is the result of a decomposition of coagulable nitrogen in the

[15] Jacoby, M., Ueber die fermentative Eiweissspaltung und Ammoniakbildung in der Leber, *Zeit. f. physiol. Chem.*, 1900, xxx, 149.

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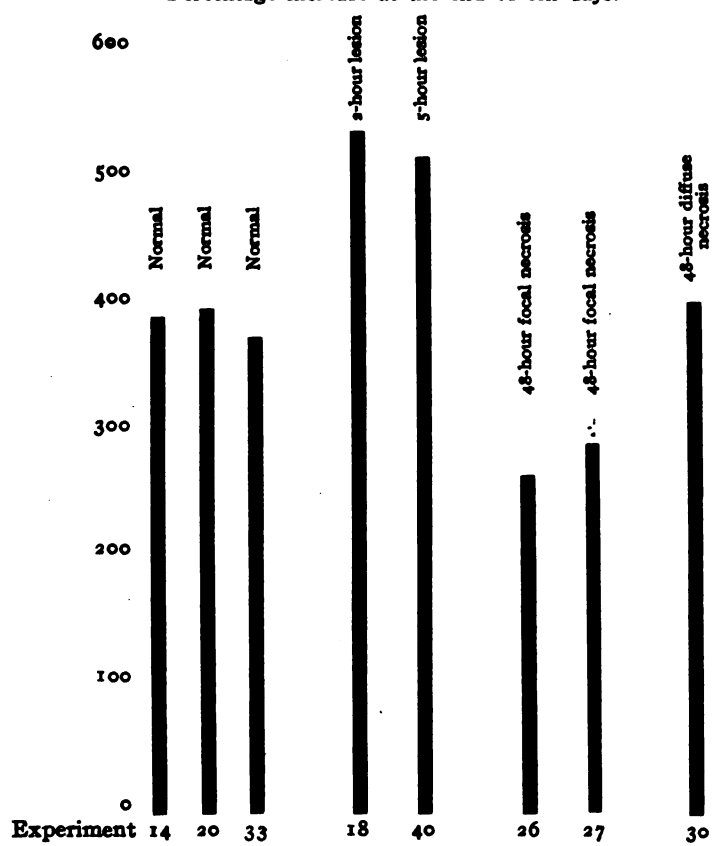
cell. That is deamidization of the amino-acids and the splitting of urea does not take place to any greater extent in the necrotic tissue undergoing autolysis than it does in the normal.

Separate Ammonia Determinations.—These experiments were some of the earlier ones performed and were carried out after the fashion of the investigations reported by Jacoby. A weighed amount, 200 grams, of the finely divided fresh liver tissue was made up to 600 cubic centimeters with distilled water and the well-mixed fluid divided into twelve equal parts. Four of these samples were sterilized immediately for controls. Two were analyzed at once as initial controls, while two, for the purpose of final controls, were placed with

TABLE II.

Ammonia.

Percentage increase at the end of ten days.



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the remainder of the portions in the thermostat. At varying periods, duplicate samples were removed for analysis. The ammonia was determined according to a modification of Shaffer's method for the urine. The accompanying diagram indicates in a schematic way the results of the experiments.

It is somewhat difficult to make comparison of these results with those just reported in the partition series since we have no determination of the amount of non-coagulable nitrogen at the various periods; hence the figures represent only the percentage increase of ammonia nitrogen based on its amount in the control sample. Although Jacoby gives in his tables only the amount of ammonia nitrogen formed without taking into consideration the question of dry solids and nitrogen of the dry residue, a recalculation of his figures from average results of our normal livers indicates that more ammonia nitrogen was formed in our experiments than in his. On the other hand, however, our figures are not as high as those reported by Soetbeer.[16] In opposition to the partition series, our figures indicate a larger amount of ammonium compounds in the initial control sample of the normal tissue than in those with varying degrees of necrosis and degeneration. This seeming anomaly we are unable to understand or explain. As, however, the percentage increase figures upon which the diagram is calculated are based upon the initial control as zero, the variable and anomalous control factor is excluded.

Considered in this way it will be seen that the three normals showed an increase of ammonia-nitrogen over the control of from 378 to 396 per cent., an agreement which serves well as a basis for comparison of the experiments on necrotic and degenerated tissue. In the case of the focal necroses the increase is less than the normal, amounting only to 265 to 290 per cent. On the other hand, the diffusely necrotic tissue evidenced the same power to produce ammonia-forming compounds as the normal. In the two samples of congestion and thrombosis, the lesion being of two to five hours' duration, more ammonia was produced than in the normal. These results would seem to indicate that during the initial stage of the process when the liver is intensely congested an increase in ammonia output must occur. This, however, is not supported by our metabolism experiments.[17]

[16] Soetbeer, F., Ueber einen Fall von akuten Degeneration des Leberparenchyms, *Arch. f. exper. Path. u. Pharm.*, 1903, l, 294.

[17] See third paper of this series "Nitrogenous Metabolism."

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Uric Acid.—The investigation concerning uric acid has yielded results of not sufficient interest for presentation in a table. The only point of importance is that a gradual diminution occurs which ceases on the third day. Since in the autolysis of uric acid ammonia is formed, this factor must influence to a slight extent the increase in ammonia observed in the partition experiments.

Arginase.—In the endeavor to explain the results in connection with the hexon bases, reported in the first paper of this series, a few experiments were conducted in the attempt to prepare from normal and necrotic livers an active substance, according to the method of Kossel and Dakin,[18] which would hydrolyze arginin into ornithin and urea. Preparations were made by both the ammonium sulphate and acetic acid-ether methods outlined by these investigators and solutions of these were added in aliquot parts to an arginin solution of known strength. The determinations were made sometimes upon the phosphotungstic precipitate, sometimes upon the filtrate from this and once upon both. The aliquots were allowed to autolyze for one, three and five days and controls were done at the beginning and at the end of the experiment.

TABLE III.

Arginase.

Experiment.	Lesion.	Method of Preparation.	Estimation on Phosphotungstate.	c.c. N/10 Acid.			
				Control.	1 day.	3 days.	5 days.
15	Normal.	¾ Saturation $(NH_4)_2SO_4$ precipitate.	filtrate.	1.6	2.65	2.75	2.65
15	Normal.	ditto.	filtrate.	4.55	5.95	6.25	6.80
15	Normal.	ditto.	precipitate.	5.75	4.45	4.25	3.65
19	Normal.	ditto.	precipitate.	4.50	3.40	5.00	5.65
42	Normal.	Extraction acetic acid.	filtrate.	5.20	4.45	4.15	4.30
18	2 hours.	Complete saturation $(NH_4)_2SO_4$ precipitate.	precipitate.	11.45	12.10	12.40	9.90
40	5 hours.	Extraction acetic acid.	filtrate.	5.40	4.65	5.30	4.40
16	Focal necroses.	Complete saturation $(NH_4)_2SO_4$ precipitate.	precipitate.	6.75	6.70	6.55	5.70
28	Diffuse necrosis	ditto.	precipitate.	6.10	6.90	6.95	6.10
28	Diffuse necrosis.	Extraction dilute HCl.	precipitate.	8.05	9.80	8.45	8.60

[18] Kossel, A. and Dakin, H. D., Ueber die Arginase, *Zeit. f. physiol. Chem.*, 1904, xli, 321. Weitere Untersuchungen ueber fermentative Harnstoffbildung, *ibid.*, 1904, xlii, 181.

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Our results in regard to the normal liver agree with those of Kossel and Dakin. The preparations from necrotic livers gave negative or doubtful results, thus affording valuable confirmatory evidence of the position which we assumed as a result of our work upon the hexon bases, namely, that in extreme diffuse necrosis where large areas remote from the circulation are undergoing necrosis there occurs a marked increase in hexon base content of the tissue. In such areas, evidently, the arginin is not split up to any noticeable extent. The experiments of Wakeman[19] do not show the presence of arginin to the marked extent which the author claims, as we have explained in our discussion of the hexon bases.[20]

The table shows that of the ten preparations made from seven different livers, three normal, two necrotic and two with thrombosis, only one, the normal (15), showed any activity. In the others either no results were obtained or were so irregular that the experiments may be considered as negative.

In this one experiment with normal liver in which the precipitate obtained by complete saturation of the three-quarter saturated filtrate with ammonium sulphate was employed, the nitrogen of the filtrate from the phosphotungstic precipitate showed a gradual increase presumably due to the autolysis of the arginin added. These results would indicate that an active arginase can be obtained only from normal tissue. This is in complete accord with the results reported in the paper on the hexon bases in which it is shown that during the autolysis of necrotic liver tissue an increase in the hexon base content of the cell occurs.

Leucin and Tyrosin.—In view of the well-recognized presence at times of monamino-acids in the urine of individuals suffering with hepatic disorders, particularly acute yellow atrophy, and of the varying results reported by the different observers in regard to the question of the presence of these compounds in the liver tissue, it seemed advisable to examine the urine and the liver of the animals under observation as to the presence of leucin and tyrosin.

It would appear to be unnecessary for us to enter into a dis-

[19] Wakeman, A. J., On the Hexon Bases of Liver Tissue under Normal and Certain Pathological Conditions, *Jour. of Exper. Med.*, 1905, vii, 292.

[20] See first paper of this series, "Hexon Bases."

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cussion of the older literature concerning the variation in the results as to the presence or absence of leucin and tyrosin in the urine under many pathological conditions. This subject has been well discussed by Ewing and Wolf,[21] who conclude that the differences observed are most probably due to faulty methods of technique and of confirmation. Of the recent work, to which this criticism cannot properly be applied is that of Taylor,[22] who found these monamino-acids present in the liver of acute yellow atrophy as well as in that of probable chloroform poisoning. In both instances, supposedly, necrosis of varying degree had taken place. Wells[23] in a preliminary communication confirms these results for acute yellow atrophy. On the other hand, however, in other conditions to which he gives the general term of "degeneration," Taylor failed to find these substances. Again leucin and tyrosin usually appear in the urine of persons or animals poisoned with phosphorus and this fact has been associated with the occurrence of the well-known hepatic changes, chiefly fatty infiltration, which are known to occur in this condition.

The recent method devised by Fischer and Bergell, in which β-naphthalin sulphochloride is employed, and Abderhalden and Barker's modification of Fischer's esterification method are so time-consuming that we decided that for the purpose in view, the simpler methods were of sufficient accuracy to warrant their use. Ewing and Wolf in the paper mentioned above criticize severely the lead acetate method, originally employed by Frerichs and Städeler. They claim that the microscopic demonstration of leucin and tyrosin by this procedure is unreliable and the crystals supposed to be leucin may be in reality urates or urea. We have used a modification of the lead acetate method in which after the removal of the excess of lead by means of hydrogen sulphide

[21] Ewing, J. and Wolf, C. G. L., The Clinical Significance of the Urinary Nitrogen, *Amer. Jour. of the Med. Sciences*, 1906, cxxxi, 751.

[22] Taylor, A. E., Ueber das Vorkommen von Spaltungsprodukten der Eiweisskorper in der degenerirten Leber, *Zeit. f. physiol. Chem.*, 1902, xxxiv, 580. On the Occurrence of Amino-acids in Degenerated Tissue, *Univ. of California Publications*, 1904, i (Path.), 43.

[23] Wells, H. G., The Composition of the Liver in Acute Yellow Atrophy. Communication read at the first meeting of the Amer. Soc. of Biol. Chemists, Washington, May 8, 1907.

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the filtrate is evaporated to dryness and the residue extracted with several portions of absolute alcohol to remove the urea, after which it is treated with repeated portions of ammoniacal absolute alcohol. The united extracts are allowed to evaporate almost to dryness, when characteristic crystals appear, if leucin or tyrosin is present in the original material. When sufficient quantities were present these microscopic findings were controlled by the usual chemical tests. We feel reasonably sure that the substances upon which we have based the following results were leucin and tyrosin.

TABLE IV.

Leucin and Tyrosin in the Urine.

Experiment.	Lesion.	Leucin.	Tyrosin.	Urine of
2	No necroses.	—	+	4th day.
34	No necroses.	+ + +	+	1st and 2d day.
1	Focal necroses.	+	+	1st day.
5	Focal necroses.	—	+	1st day.
23	Focal necroses.	+ +	+	1st and 2d day.
2	Diffuse necrosis.	—	+	1st day.
48	Diffuse necrosis.	—	+ +	1st and 2d day.
51	Diffuse necrosis.	—	+ +	2d and 3d day.

TABLE V.

Leucin, Tyrosin and Proteoses in the Liver.

Experiment.	Lesion.	Leucin.	Tyrosin.	Proteoses.	Age of Lesion.
16	Focal necroses.	—	+	+	48 hour.
32	Diffuse necrosis.	—	+	+	26 hour.
48	Diffuse necrosis.	—	+ +	+	48 hour.
51	Diffuse necrosis.	—	+ +	+	48 hour.

The table giving the results of the examinations of the urine shows that there is no regularity in the occurrence of these compounds. The type of the lesion has apparently no relation to the amount eliminated and the results presented justify the general concensus of current opinion that the appearance of these compounds is not to be regarded as pathognomonic of any one condition such as acute yellow atrophy or phosphorus or chloroform poisoning. In addition to the positive results presented in the table the urine of nine other animals was examined with negative results. In five of these the liver showed necroses, in four none.

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The results of the examination of the liver substance point to the occurrence of tyrosin in larger amounts when the lesion was almost pronounced; thus in each of three livers with diffuse necrosis it was present, but in only one of the five examples of focal necroses did it occur. A normal liver and also one with degeneration but no necroses were likewise negative. In no condition did we find leucin. In four livers with extensive necrosis proteoses were found in considerable quantities while a normal liver yielded none. All of this is in agreement with the variable results of Taylor mentioned elsewhere.

It is evident, therefore, that leucin and tyrosin may be formed during the autolysis of the hepatic tissue, but their appearance in the urine or detection in the liver is dependent upon the condition of the hepatic cells not involved in the lesion. If these cells can take care of large quantities of monamino-acids carried to them normally by the portal vein we see no reason why, if they are present in sufficient numbers and properly functionating, that they should not react in the same way with the same acids formed during the autolysis. The appearance of these monamino-acids under any condition then would depend upon the quantitative relation of the necrosis to the actively functionating cells which are unaffected by the lesion.

Of considerable interest in connection with the finding by Salkowski[24] in the urine of various pathological conditions, more particularly a case of yellow atrophy, of an increased amount of nitrogen precipitable by alcohol, is the fact that although in the normal liver the residue remaining after the extraction with absolute alcohol and ammoniacal alcohol is small in amount, in the case of the necrotic tissues this amount is markedly increased. We have examined the residue as to its character and find that it consists mainly of proteoses. The removal of these compounds by way of the blood-stream would cause an increase in the urine of undetermined nitrogen usually ascribed to amino-acids. This occurrence explains those conditions characterized by a high rest-nitrogen without the presence of monamino-acids.

[24] Salkowski, E., Zur Kenntnis der Alkoholunlöslichen bzw. kolloidalen Stickstoffsubstanzen im Harn, *Berl. klin. Woch.*, 1905, xlii, 1581, 1618.

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SUMMARY.

1. The presence of blood serum has a decided inhibitory effect on autolysis. Thus in the normal unwashed organs the non-coagulable nitrogen increase was 100 to 300 per cent., while in the washed it amounted to 450 per cent. The washed necrotic livers showed an increase of from 600 to 850 per cent., while that of the unwashed necrosis was only slightly above the normal unwashed.

2. While the initial amount of non-coagulable nitrogen varies it is greater in those livers showing the more extensive forms of necrosis. The final amount of autolysis is also greatest in livers of this type. As regards the rate of autolysis fifty per cent. of the total occurs in the first day in the normal and in all types of lesions both washed and unwashed. The maximum is usually reached on the third day in the unwashed, while in the washed there is a continued increase to the eighth day. At this time in the necrotic livers about two to three times as much of the total nitrogen is in the form of non-coagulable nitrogen as in the normal.

3. In the necrotic tissue the initial controls show the content of monamino-acids, with one exception, to be practically doubled. In the washed necrotic the final amount is seventy per cent. of the total nitrogen against forty-six to fifty-seven per cent. in the washed normal. In all cases the monamino-acid nitrogen runs parallel to the nitrogen in non-coagulable form, but in relation to the total nitrogen it shows a greater increase in the washed than in the unwashed organs.

4. The ammonia production in the necrotic livers as shown by the partition experiments is greater than that in the normal and this increase corresponds to that of the non-coagulable nitrogen. In the experiments concerning the absolute production of ammonia in the presence of serum a greater amount was produced in the two and five hours' lesions than in the normal livers. On the other hand, the forty-eight hour diffuse necrosis equaled the normal and the focal fell below.

5. Arginase was obtained from normal but could not be isolated from necrotic livers.

6. No constant relation could be demonstrated between the anatomical lesion in the liver and the presence of leucin and tyrosin in the urine. Leucin was found occasionally in the

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urine, but never in the liver. On the other hand, tyrosin was constantly present in livers with diffuse but rarely in those with focal necrosis. In the instances of diffuse necrosis in which the liver and urine of the same animal were examined tyrosin was found in both.

7. The presence of large amounts of proteoses in the necrotic liver indicates that the elimination of these substances (colloidal nitrogen of Salkowski) under such circumstances may account for a part of the total nitrogen of the urine usually attributed to the monamino-acids.

EXPERIMENTAL LIVER NECROSIS; III. NITROGENOUS METABOLISM.[1]

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We present here the results of experiments carried out upon dogs in which the general state of the nitrogenous metabolism of the animals was studied before and after the injection of hemotoxic immune sera. As has been stated elsewhere[2] the important organic lesion produced by such sera is a hepatic necrosis either focal or diffuse, according to the amount and strength of the serum employed. Such an experimental lesion seemed peculiarly adapted to the study of the function of the liver in general metabolism and of certain peculiar metabolic derangements which have an analogy to those noted in eclampsia, chloroform poisoning, vomiting of pregnancy and acute yellow atrophy. It must be clearly borne in mind, however, that this experimental method of producing hepatic necrosis allows of the infliction upon the liver of a single injury, in point of time, which if not followed by death is rapidly repaired and which is almost without other disturbing factors. Hence metabolic variations may

[1] Conducted under grants from the Rockefeller Institute for Medical Research. Read before the American Association of Pathologists and Bacteriologists, Washington, May 7, 1907. Published also in *Journal of Experimental Medicine*, 1907, ix, 552.

[2] See first paper of this series, "The Hexon Bases."

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be transient and last but one or two days, and for this reason the resulting disturbance is not comparable to that produced by a continually acting cause with progressive lesion.

The experiments were carried out upon dogs kept in the usual well-ventilated metabolism cages and fed upon a purin-free diet of casein, cracker dust and lard. The amounts of the three dietary constituents varied for the different animals. They were calorifically sufficient and so regulated that the animal finally came into nitrogen equilibrium. The dogs were catheterized at the end of each twenty-four hour period and the urine thus obtained, added to that voided naturally. This was at all times carefully preserved from changes of any kind until the analytic work was completed. To the total twenty-four elimination was added distilled water to make the volume up to 800 cubic centimeters. When hemoglobinuria or albuminuria caused the appearance of proteid in the urine this was removed by heat and acetic acid, the coagulum being thoroughly boiled out with water and the washings added to the urine.

Upon these twenty-four hour samples the following determination was made: total nitrogen by the Kjeldahl-Gunning method; ammonia by the Shaffer method; urea by the Mörner-Sjoquist method; uric acid by the Hopkins-Folin method and creatinin by Folin's colorimetric adaptation of Weyl's qualitative test. The difference between the sum of these various factors and the total nitrogen is given as rest or undetermined nitrogen. Kynurenic acid was also looked for qualitatively in order to obtain evidence as to variations in the output of this substance.

The general procedure in these experiments was to place the animal upon nitrogen equilibrium and to conduct control determinations for a period of three days, after which the animal was injected with either normal or toxic sera and the experiment allowed to continue until death ensued or the metabolism had regained its normal level as shown by the control period. It is obvious that in experiments of this character it becomes extremely difficult, if not impossible, owing to variance in the toxicity of the sera and the susceptibility of the animals, to regulate the severity of the lesion, especially as the degree of the latter can be determined only by post-mortem examination. This fact prohibits the production in any two experiments, no matter how carefully planned, of absolutely comparable pathological conditions. This difficulty is brought out by the fact that

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although each new lot of serum was tested for lethal action on dogs of approximately the same weight and conditions as those prepared for the experiment, only six out of twelve of the latter survived the first twenty-four period. These six, with a control dog receiving normal serum, constitute the experiments on which this communication is based.

These may be divided into four groups: one injected with normal serum in which no histological change took place; one with a weak toxic serum which caused no necrosis, but an extensive granular and vacuolar degeneration; four with toxic sera causing more or less extensive focal necroses and one with toxic serum producing diffuse necrosis.

TABLE I.

(*Dog 18, normal serum.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Nov. 10	6.51	4.99 76.8	0.556 8.5	0.018 0.28	0.677 10.4	0.269 4.0	
11	6.09	4.81 78.9	0.492 8.1	0.013 0.21	0.633 10.4	0.142 2.4	
12	6.52	5.25 80.5	0.493 7.6	0.020 0.30	0.607 9.3	0.150 2.3	Injected 12 M. Dose: 1:738. Vomited.
13	6.60	5.06 76.6	0.510 7.7	0.017 0.26	0.576 8.7	0.437 6.7	
14	6.06	4.72 77.8	0.482 8.0	0.021 0.34	0.539 8.9	0.298 5.0	

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

Table I shows the result of the injection of normal serum. With this may be compared also Tables VI and VII, in which it is seen that the toxic serum was preceded by an injection of normal serum. In two of these the dose[3] of the normal serum was greater than that of any injection of toxic serum. It will be seen that it was practically without effect although in Dog 48 (Table VI) a slight increase in the output of total nitrogen was evident. A consideration of the nitrogen partition indicates, however, that this increase is mainly at the expense of the rest-nitrogen and is to be explained by traces of foreign proteid of the rabbit's serum injected, too small to be removed by the ordi-

[3] The figures representing dosage, for example 1:600, indicate that the dose was in the proportion of one cubic centimeter of serum to 600 grams of body weight.

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nary methods. We possess, therefore, a series of controls upon which to base our conclusions concerning the effect of the toxic sera.

Table II gives the figures obtained as the result of injecting a weak serum,[4] which caused extensive hepatic degeneration of the granular and vacuolar type but no necrosis.

TABLE II.

(*Dog 12, Degeneration, No Necrosis.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Oct. 15	4.33	3.67 84.5	0.157 3.6	0.006 0.14	0.302 7.0	0.195 4.76	
16	3.77	3.24 85.7	0.131 3.5	0.005 0.13	0.285 7.6	0.109 3.07	
17	3.76	3.29 87.3	0.120 3.1	0.004 0.13	0.284 7.6	0.062 1.87	
18	3.16	2.72 87.1	0.104 3.3	0.004 0.13	0.241 7.6	0.060 1.87	
19	4.23	3.56 84.1	0.090 2.1	0.004 0.09	0.315 7.5	0.261 6.21	Injected 4.30 P. M.; weak toxic serum; dose 1:715.
20	3.37	2.66 78.9	0.165 4.9	0.003 0.09	0.288 8.5	0.254 7.66	
21	3.19	2.69 84.3	0.161 5.1	0.006 0.19	0.268 8.4	0.065 2.01	
22	3.02	2.60 86.1	0.122 4.0	0.002 0.06	0.260 8.7	0.036 1.14	Killed.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

It is seen that a slight but transient rise in the total nitrogen occurred. A small part of this increase is attributable to the foreign proteid injected, with a corresponding rise in the undetermined nitrogen, both in absolute and percentage amounts. The absolute amount of urea nitrogen increased during the first twenty-four hours after injection but not in sufficient quantities to keep pace with the increase in total nitrogen, hence a percentage decrease occurred. The following day both the percentage and absolute amounts diminished markedly to be followed on the succeeding days by return to the normal percentage of urea output. The absolute quantity remained low since the total nitrogen did not return to normal. The ammonia output during the twenty-four hours succeeding the injection suffered a decided

[4] The serum of a rabbit which was not bled until six weeks after immunization against dog's blood. Sera obtained so long after injection frequently show diminished hæmagglutinative and hæmolytic power.

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diminution both in percentage and absolute figures. This decrease was exceedingly transient, since on the succeeding days the reverse occurred and both the absolute and percentage figures went much above the normal. The uric acid and creatinin showed no change but the rest-nitrogen increased considerably on the first and second days following the injection.

The reaction[6] for kynurenic acid was positive on the day subsequent to the injection and passed off gradually. This would indicate an increase in proteid destruction.[7]

Of most importance is the diminution in the percentage of the total nitrogen eliminated as urea associated with a somewhat corresponding increase in the percentage output of ammonia and rest-nitrogen. This is the urinary picture which recently has been described as associated with the hepatic disorder supposed to underly the symptoms of chloroform poisoning, toxemia of

TABLE III.

(*Dog 25, Focal Necroses.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid [5]	Creatinin.	Undetermined Nitrogen.	Notes.
Dec. 2	4.77	3.55 76.5	0.443 9.1		0.405 8.4	0.372 6.0	
3	5.42	4.39 81.0	0.507 9.4		0.362 6.7	0.161 3.3	
4	5.24	4.11 78.4	0.440 8.4		0.298 5.7	0.392 7.5	
5	4.97	3.86 77.6	0.421 8.5		0.335 6.7	0.354 7.2	
6	6.02	4.68 77.4	0.496 8.2		0.362 6.0	0.482 8.4	Injection 2:30 P. M.; toxic serum dose 1: 1000. Vomited.
7	5.85	4.77 81.5	0.443 7.6		0.351 6.0	0.286 4.9	Hburia.
8	5.92	4.95 83.6	0.313 5.3		0.323 5.3	0.334 5.8	Hburia.
9	9.33	7.66 82.1	0.587 6.3		0.430 4.6	0.653 7.0	Hburia.
10	6.46	5.40 83.5	0.376 5.8		0.360 5.6	0.324 5.1	
11	8.15	7.16 87.8	0.404 4.9		0.368 4.5	0.218 2.8	
12	8.22	7.07 86.0	0.461 5.6		0.366 4.5	0.323 3.9	No food taken; killed.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

[5] Amounts so small that they were not calculated.

[6] Treatment of the urine with bromine water.

[7] Mendel, L. B. and Jackson, H. C., On the Excretion of Kynurenic Acid, *Amer. Jour. of Physiol.*, 1898, ii, 1.

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TABLE IV.

(*Dog 43, Focal Necroses.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Feb. 2	7.74	6.31 81.5	0.444 5.7	0.018 0.23	0.417 5.4	0.551 7.2	
3							Feces mixed with urine.
4	6.95	5.50 79.1	0.406 5.8	0.013 0.17	0.338 4.9	0.693 10.0	
5	6.45	5.37 83.2	0.335 5.2	0.015 0.23	0.280 4.3	0.450 7.1	Injected 10:30 A. M.; toxic serum dose 1: 1738. Vomited.
6	9.91	8.48 85.5	0.478 4.8	0.073 0.73	0.343 3.5	0.836 8.5	Injected 3 P. M.; toxic serum; dose 1: 1200.
7	10.56	8.88 84.1	0.578 5.5	0.045 0.42	0.405 3.8	0.652 6.2	
8	7.65	6.31 82.5	0.479 6.2	0.009 0.12	0.386 5.0	0.466 6.2	
9							Urine lost.
10	4.85	3.84 79.2	0.288 5.9	0.007 0.14	0.341 7.2	0.374 7.6	Killed.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

pregnancy and like conditions and which will be discussed more in detail after our results have been completely given.

Tables III, IV, V, VI and VII present the results of the experiments in which a true necrosis, either focal or diffuse, was obtained.

In these experiments the injection of the toxic sera[8] was always quickly followed by a more or less marked increase in the elimination of total nitrogen which *persisted* for several days. During the first or second twenty-four hour period, after injection, occurred a slight increase in the percentage of urea nitrogen (three to five per cent.) which was followed on the succeeding days by a drop to normal, and in one experiment below normal. The ammonia nitrogen percentage of the total nitrogen diminished gradually after the injection and reached its lowest point about the second or third day, after which, in some cases, as in Dogs 49 and 43, it returned to normal; in others, as in Dogs 25, 45, and 48, it remained low. The more advanced the repair

[8] In three of these experiments the first injection was followed by a second after a varying interval. This fact renders the figures after the time of the second injection less comparable.

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at the time of death, the nearer the percentage of ammonia nitrogen had returned to the normal.

The uric acid nitrogen suffered a marked, though transient, increase.[9] In the three experiments where successive injections were given, the second injection in each instance caused an increase of uric acid on the following day after which it returned to normal.

The absolute creatinin nitrogen output was noticeably augmented after injection; this increase, however, was not quite in the same proportion as the total nitrogen, hence the creatinin nitrogen per cent. of the total tended at times to show a slight diminution.

The undetermined or rest-nitrogen which in a general way may be said to indicate the output of amino-acids, polypeptids or proteose-like bodies[10] also underwent a decided increase after injection.

An increase in kynurenic acid elimination after injection was

TABLE V.

(*Dog 45, Focal Necroses.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Feb. 3	6.70	5.50 82.1	0.342 5.1	0.014 0.21	0.274 4.1	0.570 7.5	
4	6.57	5.37 81.7	0.491 7.5	0.013 0.20	0.296 4.5	0.400 6.1	
5	6.43	5.05 78.5	0.452 7.0	0.012 0.18	0.274 4.1	0.642 10.2	
6	6.52	5.33 81.7	0.455 7.0	0.013 0.20	0.265 4.1	0.457 7.0	Injected 10 A. M.; toxic serum; dose 1:1500.
7	8.99	7.51 83.5	0.560 6.2	0.105 1.17	0.359 4.0	0.456 5.1	
8	7.97	6.25 78.4	0.524 6.6	0.010 0.13	0.300 3.9	0.886 11.0	Injected 10 A. M.; toxic serum; dose 1:1000.
9	5.30	4.01 75.6	0.441 8.3	0.055 1.04	0.298 5.7	0.928 9.4	
10	10.30	8.20 79.6	0.646 6.3	0.030 0.28	0.349 3.4	1.075 10.4	
11	8.37	6.71 80.2	0.598 7.1	0.021 0.25	0.313 3.7	0.728 8.8	
12	7.45	5.99 80.0	0.447 6.0	0.009 0.12	0.326 4.5	0.678 9.4	Killed.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

[9] For a detailed discussion of this subject see fourth paper of this series, "Nuclein Metabolism."

[10] Salkowski, E., Zur Kenntnis der Alkoholunlöslichen bzw. colloidalen Stickstoffsubstanzen im Harn, *Berl. klin. Woch.*, 1905, xlii, 1581, 1618.

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TABLE VI.

(*Dog 48, Diffuse Necroses.*)

Date.	Total Nitrogen.	Urea.*	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Feb. 19	6.80	5.90 86.7	0.374 5.5	0.018 0.26	0.373 5.5	0.135 2.0	
20	6.55	5.53 84.4	0.360 5.5	0.018 0.27	0.364 5.6	0.278 4.2	
21	6.38	5.41 84.8	0.358 5.6	0.024 0.37	0.326 5.2	0.228 4.0	Injected 5 P. M.; normal serum; dose 1: 600.
22	7.00	5.76 82.3	0.406 5.8	0.024 0.34	0.338 4.8	0.472 6.8	
23	6.53	5.50 84.2	0.376 5.8	0.021 0.32	0.326 5.0	0.307 4.7	
24	6.10	5.00 82.0	0.400 6.6	0.018 0.30	0.314 5.1	0.368 6.0	Injected 10 A. M.; toxic serum; dose 1: 1155.
25				0.036			Vomitus mixed with urine.
26	8.78	7.58 86.3	0.365 4.1	0.018 0.20	0.345 4.0	0.472 5.4	
27	9.11	6.80 (?) 76.4	0.551 6.0	0.018 0.20	0.349 3.8	1.392 (?) 13.6	Injected 10 A. M.; toxic serum; dose 1: 600. Vomited. Hburia.
28	11.12	9.24 83.1	0.418 3.8	0.130 1.17			Vomiting; refused food.
Mar. 1				0.083			Died.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

noticed at times, but this was slight at the best and in no way corresponds to the increase which occurs after the administration of phosphorus, phlorhizin and large quantities of meat. In these latter instances Mendel and Jackson[11] showed that the increased kynurenic acid output was associated with augmented endogenous or exogenous destruction of proteid material containing the tyrosin nucleus.

As has already been stated, we believe that the effect of the blood changes produced by the serum is directed almost entirely upon the liver and represents a single attack upon this organ. Two coincident conditions, which however do not affect the results in any manner, require perhaps a brief notice. In the first place vomiting usually occurs and persists for a short time, five to ten minutes, after the injection. The feeding and injection were so arranged that nothing was lost in this manner and

[11] Mendel, L. B. and Jackson, H. C., On the Excretion of Kynurenic Acid, *Amer. Jour. of Physiol.*, 1898, ii, 1.

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TABLE VII.

(*Dog 49, Focal Necroses.*)

Date.	Total Nitrogen.	Urea *	Ammonia.	Uric Acid.	Creatinin.	Undetermined Nitrogen.	Notes.
Feb. 22	5.24	4.33 82.6	0.366 7.0	0.021 0.40	0.215 4.1	0.308 5.9	
23	5.48	lost	0.320 5.9	0.018 9.33	0.218 4.0		
24	5.46	4.41 80.8	0.345 6.3	0.021 0.38	0.208 3.8	0.476 8.7	Injected 10 A. M.; normal serum; dose 1: 600.
25				0.018			Vomitus mixed with urine.
26	5.25	4.34 82.7	0.297 5.7	0.021 0.40	0.194 3.7	0.398 7.5	Trace albumin.
27	5.63	4.77 84.8	0.320 5.7	0.022 0.39	0.204 3.6	0.314 5.5	Injected 10 A. M.; toxic serum; dose 1:628. Vomited.
28	7.07	6.07 85.6	0.245 3.5	0.014 0.20	0.189 2.7	0.452 8.0	Hburia.
Mar. 1	9.14	7.56 82.7	0.270 2.8	0.029 0.32	0.225 2.5	1.056 11.7	Hburia.
2	8.45	6.98 82.6	0.428 5.1	0.017 0.20	0.221 2.6	0.804 9.5	Hburia.
3	6.97	6.04 86.6	0.370 5.3	0.022 0.31	0.214 3.1	0.324 4.7	Hburia.
4	5.70	4.92 86.3	0.366 6.4	0.020 0.35	0.196 3.4	0.198 3.6	Hburia. Killed.

* Figures in upper left-hand corner represent grams nitrogen; those in lower right-hand corner, percentage of total nitrogen.

as the vomiting also occurred when normal serum was used, with no apparent effect on the metabolism, we believe this factor may be disregarded. It has occasionally, however, caused the loss, on account of admixture of vomitus, of a day's urine.

In the second place hemoglobinuria, sometimes but not always, makes its appearance after twenty-four hours. This condition, however, could not have produced the changes in the general metabolism which we have described since in two of the experiments (43 and 45), where no hemoglobin or bile appeared in the urine, the results were the same as in those showing a well-marked hemoglobinuria. This agrees with the observations of Samuely[12] who found in experimental anemia, produced by means of pyrodin, that the appearance of hemoglobin or bile in the urine stood in no direct relationship to the changes which took place during the anemia. On the other hand, Andrea[13] in a series of experiments, in which various hemolytic substances

[12] Samuely, F., Stoffwechseluntersuchungen bei experimenteller Anämie, *Deut. Arch. f. klin. Med.*, 1907, lxxxix, 220.

[13] Andrea, P., Influenca della sostanze emolitiche sulle funzioni ureogenetica ed antitossica del fegato, *Arch. Int. de Pharmacodyn. et de Therapie*, 1905, xiv, 389.

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(phenylhydrazin, pyrogallol, p-phenylendiamin, glycerin) were administered to rabbits, has found an increase of urea after the initial injection, but a decrease of one-third after subsequent injections. The increase he explains by destruction of hemoglobin and the decrease as due to impaired hepatic function.

Another possibility, however, must also be considered. This is that the temporary anemia which is simultaneously produced as the result of the primary action of the serum on the red cells may originate changes in oxidization capable of accounting for some of the results. If the anemia were general in character and of the type which occasions a great diminished oxidative power throughout the body, such as is noticed after carbon monoxide poisoning, then we should expect to find, among other disturbances, the elimination of incompletely oxidized products of catabolism, such as lactic acid. We have searched for the appearance of this substance in the urines of five of the animals showing necrosis, but have failed to find it. This, with other facts, appear to justify the exclusion of the factor of diminished oxidation.

In this connection it is of considerable interest to note also that in the type of anemia produced by Samuely the power of the body to oxidize aromatic compounds, such as phenylalanin and cystein, was somewhat decreased, but that the metabolism in regard to the fatty amino-acids was absolutely unchanged.

Upon the whole, therefore, it seems justifiable to designate, as the main causative factor in the production of the results obtained, the necrotic lesions more or less diffusely disturbed throughout the liver.

Several attempts have been made to study the influence of hepatic necrosis upon the metabolism. Jacoby[14] was the first to study the effect of tying off the vessels supplying certain lobes of the liver. Unfortunately the animals did not survive the operation a sufficient length of time to allow observations upon the urine and he was compelled to content himself with demonstrating that products of autolysis were present in the lobes shut off from the circulation. Doyon and Dufourt[15] report

[14] Jacoby, M., Ueber die fermentative Eiweissspaltung und Ammoniakbildung in der Leber, *Zeit, f, physiol. Chem.*, 1900, xxx, 149.

[15] Doyon, M. and Dufourt, L., Contribution à l'étude de la fonction ureopoietique du foie; Effets de la ligature de l'artère hepatique et de alle de la veine porto (*Arch. de physiol. normal et path.*, 1898, S. 5, x, 522), Ref. in *Maly's Jahresbericht f. Thierchemie*, 1898, xxviii, 382.

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that upon tying off the hepatic artery they obtained a diminished formation of urea and increase in ammonia. Their results were somewhat unsatisfactory, however.

From the clinical side of the question quite recently a considerable amount of data which bears upon the question at hand has accumulated. Many investigators have studied the urinary changes occurring in certain metabolic disorders associated with hepatic diseases. Thus Schittenhelm[16] reports that in chronic diseases of the liver the ammonia output in relation to the total nitrogen elimination is increased. Axisa[17] states that in liver abscesses the same change is associated with a marked decrease in the urea percentage. Ingelrans and Dehons[18] corroborate these findings in hepatic insufficiency and claim that cirrhosis gives the same pictures as acute yellow atrophy. De Rossi,[19] on the other hand, offers evidence that not all diseases in which lesions of the liver are present show this altered relation of urea to ammonia elimination and concludes that the liver is not the only seat of the formation of urea.

In regard to acute yellow atrophy, vomiting of pregnancy, eclampsia, delayed chloroform poisoning and phosphorus poisoning, recent investigations seem to show that the hepatic lesions, which are found to be present at autopsy in these conditions, are an important causative factor in the disturbance of metabolism. This disturbance shows itself in the urine by a marked diminution in the output of urea and an increase of the ammonia in relation to the total nitrogen elimination. Williams[20] assumes that the urinary picture of pernicious vomiting of pregnancy with its high percentage ammonia output is sufficiently definite to render it a valuable aid in determining the question of inducing labor. On the other hand, he contends that in the condition known as eclampsia there is a diminution in the total nitrogen and percentage urea with no very pronounced ammonia

[16] Schittenhelm, A., Zur Frage der Ammoniakausscheidung im menschlichen Urin, *Deut. Arch. f. klin. Med.*, 1903, lxxvii, 517.

[17] Axisa, E., Ueber Harnstoff und Ammoniakausscheidung im Harn bei Leberabszess, *Zent. f. innere Med.*, 1905, xxvi, 929.

[18] Ingelrans, L., and Dehons, M., La valeur clinique de quelques signes urinaires considérés comme révélateurs de l'insuffisance hepatique, *Arch. de med. exper. et d'anat. path.*, 1903, xv, 188.

[19] De Rossi, S., Sul valore semeiologico dell'urea et dell'ammonica nelle lesioni epatiche, *Riforma Medica*, 1904, xx, 1177.

[20] Williams, J. W., Pernicious Vomiting of Pregnancy, *Surgery, Gynecology and Obstetrics*, 1905, i, 41; *Johns Hopkins Hospital Bul.*, 1906, xvii, 71; *Amer. Jour. Med. Sciences*, 1906, cxxxii, 132.

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variation. Stone[21] believes that the vomiting of pregnancy is the result of a toxemia, the lesions of which are primarily an acute degeneration of the liver amounting sometimes to necrosis and resembling in the fatal cases those of acute yellow atrophy. Zweifel's[22] researches confirm the opinion that the causative factor in eclampsia is a diminished oxidation which shows itself in the production and elimination of considerable quantities of p-lactic acid. The increased ammonia output is the result of the neutralization of the excess of acids produced and the diminished urea is due to the removal of quantities of ammonia which normally should be synthesized into urea.

Ewing and Wolf[23] report observations made upon pregnant women from the results of which they conclude that the various conditions of eclampsia, vomiting of pregnancy and yellow atrophy are but different degrees or manifestations of the same disordered process which probably centers itself in the hepatic cells and leads to the deranged elimination of urea and ammonia. A similar disturbance of metabolism associated with necrosis of the liver, has been found by Bevan and Favill[24] in fatal chloroform poisoning.

In view of all this it can readily be seen that the concensus of opinion favors the idea that the changes in the percentage elimination of urea and ammonia which are found to occur in these various conditions are but indications of the same functional lesion which centers itself in the hepatic cell. When necrosis of the liver occurs the cells which ordinarily synthesize ammonia into urea are out of function and the ammonia elimination is increased and the urea correspondingly falls.

With a full appreciation of the necessity of caution in transscribing deductions from the results of animal experiments to the explanation of pathological variations in the human organism, we feel that our results render somewhat doubtful the relationship between the hepatic necrosis of the vomiting

[21] Stone, W. S., The Toxæmia of Pregnancy, *Amer. Gynecology*, 1903, iii, 518; Some Further Notes on the Toxæmia of Pregnancy, *Med. Record*, 1905, lxviii, 295.

[22] Zweifel, Zur Aufklärung der Eklampsie, *Arch. f. Gyn.*, 1905, lxxvi, 537.

[23] Ewing, J. and Wolf, C. G. L., The Clinical Significance of the Urinary Nitrogen, II. The Metabolism in the Toxæmia of Pregnancy, *Amer. Jour. of Obstetrics*, 1907, lv, 289.

[24] Bevan, A. D., and Favill, H. B., Acid Intoxication and Late Poisonous Effects of Anæsthetics, *Jour. Amer. Med. Assoc.*, 1905, xlv, 691.

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of pregnancy, for example, and the urinary finding of a high percentage ammonia output. Wolf[25] has already justly criticized the conclusions of Williams in this regard and emphasizes the well-known fact that equally high percentages of ammonia are to be found when for any reason, as in inanition, the nitrogen or the calorific value of the diet becomes insufficient for the replacement of the wear and tear of the cell.[26] Schittenhelm has shown the influence of diet in this connection by experiments in chronic hepatic diseases where a high ammonia output is present. He noticed that upon increasing the fat of the diet a still further increase in the elimination of ammonia occurred and believes that the ammonia offers simply an indication of the lack of normal oxidation or catabolism of the ingested fatty acids. An examination of the results presented by Williams makes it seem very plausible that the diet in his cases is not an unimportant factor in the results. The figures for the total nitrogen indicate that the patients were practically in a state of diminished nutrition even approaching inanition since the amounts fall anywhere between four to eight grams per day, and more important still, the higher the total nitrogen the lower the ammonia and *vice versa* regardless of the severity of the condition. This same criticism can also be applied to the results of Ewing and Wolf. The daily total nitrogen elimination in their experiments is quite as low as that found by Williams, hence the high ammonia can be equally well attributed in part at least, to similar causes.

The factor of low and insufficient diet was excluded in our experiments since the animals were upon exact equilibrium. We did obtain, however, severe hepatic lesions consisting of localized or diffuse necrotic areas and the ammonia output of our animals never showed more than the merest increase which was exceedingly transient. At this place emphasis must be laid upon the one experiment in which results comparable to, if not as pronounced as those of Williams and of Ewing and Wolf, were obtained. In this instance (see Table II.), however, the histological findings indicated that we were

[25] Wolf, C. G. L., The Chemistry of Toxæmias in Pregnancy, *New York Med. Jour.*, 1906, lxxxiii, 813.

[26] Folin, O., Laws Governing the Chemical Composition of Urine, *Amer. Jour. of Physiol.*, 1905, xiii, 66.

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dealing not with a lesion of necrotic character but with an extensive and diffuse degeneration.

On account of the loose use of terms in pathology, this would seem to emphasize that a clear-cut differentiation between degeneration and necrosis[37] must be made histologically if we are to correlate the results of chemical studies and histological findings. The pathological condition "degeneration" does not imply autolysis which occurs only in necrosis. It is evident that one may occur without the other and therefore that the chemistry of the cell depends on its functional activity as determined by its physical state. As a reasonable explanation of why a difference in metabolism must be expected in the conditions of degeneration as opposed to necrosis we would present the following: In a generalized hepatic degeneration the lesion affects the protoplasm of each and every cell of the whole organ without destruction of the nucleus. This degeneration may set up enzymotic disturbances, secondary in character, which are not connected directly with the actual life processes of the cell and which may readily again return to normal when the abnormal conditions of the cell are removed. Such a differentiation between the actual life processes of the cell and those of a secondary functional character finds best expression in the German words "Baustoffwechsel" and "Betriebstoffwechsel." When the disturbance of enzymotic equilibrium occurs, if we grant for the sake of argument the unproven hypothesis that the the urea formation is the result of enzymotic relations, there would take place an interference in the production of urea from ammonium compounds without an increase in the output of total nitrogen. A simple rearrangement in the partition factors would evidence itself according to which the ammonia would increase as the urea correspondingly diminished. This is exactly the condition found in our experiment with diffuse degeneration.

On the other hand, in necrosis, the individual cell is destroyed and all its functions cease. Autolysis begins in the same way as it does when death supervenes as the result of the removal of the cell from the body. Under such circumstances there occurs a true protoplasmic decomposition from

[37] See first paper of this series, "The Hexon Bases."

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which the cell can never recuperate. Here the nucleus becomes involved as is shown by the histological picture and in the urine by the occurrence of a marked increase in the elimination of uric acid, purin bases[28] and phosphorus.

In necrosis, moreover, although many individual cells are dead and have ceased to functionate, there always remain, unless the whole organ becomes necrotic, in contradistinction to the condition of degeneration, many normal cells, ready and capable of assuming in a vicarious manner the function of those already dead. This "factor of safety" in the liver is well demonstrated by the partial extirpation experiments of Ponfick, while the power of other organs to assume the urea-forming function is shown by the numerous Eck fistula experiments.

In necrosis, therefore, all that is expected as a urinary finding is the appearance of an increase in the total nitrogen output and of the abnormal products of autolysis such as proteoses, polypeptids and amino-acids; and even these latter, in scattered focal necrosis, need not necessarily appear since as very little liver tissue is destroyed the remaining normal cells still possess the power of splitting these substances, formed by cellular digestion, just as they do similar products of intestinal digestion brought to them by the portal[29] vein.

Our results substantiate this theoretical expectation. In the experiments with diffuse necrosis a marked and continued augmentation in the total nitrogen and urea elimination occurred as the result of the removal of the products of autolysis. The diminution in the ammonia output may be ascribed naturally to the increase in the proteid catabolism. Finally the increase in undetermined nitrogen is not definitely to be ascribed to the amino-acids ordinarily considered in this connection since we have not found leucin and tyrosin in the urine in amounts which would compare with those found in acute yellow atrophy.[30] It is to be considered rather as in

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[28] For a detailed discussion of this subject see fourth paper of this series, "Nuclein Metabolism."

[29] Freund, E. and Tœpfer, G., Ueber den Abbau des Nahrungseiweisses in der Leber, *Zeit. f. exp. Path.*, 1906, iii, 632.

[30] Riess, L., Phosphorvergiftung und Leberatrophie, *Berl. klin. Woch.*, 1905, xlii (Ewald Festnummer 44 a, 54).

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the "colloidal" form as described by Salkowski and Mancini.[31]

SUMMARY.

1. In focal and diffuse necroses of the liver due to hemotoxic sera there occurs an increased elimination of total nitrogen with a corresponding augmented output of urea. The ammonia excretion becomes slightly diminished at first, but later rises somewhat above normal. The undetermined nitrogen is markedly increased.

2. In diffuse degeneration with no necrosis on the other hand only a slightly increased output of total nitrogen is evident. A rearrangement of the urea-ammonia proportion occurs in that the ammonia excretion is augmented while the urea elimination is correspondingly diminished. The undetermined nitrogen rises but little.

3. In control experiments with normal serum no effect is produced.

4. These results would appear to indicate that in lesions characterized by uniform degeneration of the liver parenchyma, in contradistinction to necrosis, there occurs no increased nitrogen elimination but merely a disturbance of the urea-forming function of the cell without the appearance in the urine of products of autolysis. On the other hand in necrosis, of even considerable extent, the total-nitrogen is greatly augmented, as is also the rest-nitrogen; while the production of urea, on account of the persistence of normally functioning liver cells, remains relatively unchanged.

This "factor of safety"[32] possessed by the liver is, we think, one of the most important results brought out in this investigation and must be given great weight in any consideration of the chemistry of hepatic disturbances.

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[31] Mancini, S., Studi un nuovo segno per la diagnosi di insufficienza epatica; Contributo allo studio dell'azeta colloidale nelle urine normali e pathologiche, (*Arch, di farmocol. speriment,* 1906) Ref. in *Biochem. Cent.*, 1906, v, 549.

[32] Meltzer, S. J., The Factors of Safety in Animal Structure and Animal Economy, *Jour. of Amer. Med. Assoc.*, 1907, xlviii, 655.

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EXPERIMENTAL LIVER NECROSIS; IV. NUCLEIN METABOLISM.[1]

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The experiments here detailed were undertaken for the purpose of determining the process or processes intimately concerned in the increased elimination of uric acid which, as has been shown elsewhere,[2] accompanies the augmented output of total nitrogen when hemotoxic serum is injected. The fact that the principal lesion produced by the toxic serum is in the liver lends peculiar interest to the problem, in view of the important part which this organ is supposed to play in the formation of endogenous uric acid. The direct object of the experiments was to determine whether the increased elimination of uric acid in dogs under these conditions was the result of the breaking down of nuclear material during the necrosis which follows the injection, or whether it signified simply a diminished oxidative power on the part of the hepatic cell by which the uric acid normally oxidized to simple complexes is eliminated unchanged. Or, more concisely, does an actual increase in the production of uric acid from the nucleic acid of the decomposed nuclei cell occur or is there a simple rearrangement of enzymotic equilibrium by which less uric acid is decomposed than normally.

Schittenhelm[3] has isolated two enzymes from the spleen and liver, one of which causes a hydrolytic splitting off of the amino group of guanin and adenin transforming these bodies thereby into xanthin[3] and hypoxanthin respectively; the other an oxydase, xantho-oxidase (Jones), oxidizes the latter compounds into uric acid. Since adenin, guanin, xan-

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[1] Conducted under grants from the Rockefeller Institute for Medical Research. Published also in *Journal of Experimental Medicine*, 1907, ix, 569.

[2] See third paper of this series "Nitrogenous Metabolism."

[3] Schittenhelm, A., Ueber die Harnsäurebildung in Gewebsauszügen, *Zeit. f. physiol. Chem.*, 1904, xlii, 251; Ueber die Harnsäurebildung und die Harnsäurezersetzung in dem Auszügen der Rinderorgane, *ibid.*, 1905, xlv, 121.

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thin and hypoxanthin are found in varying amounts in the different nucleic acids which give character to the nucleoproteid of the nucleus we have a fairly definite process by which uric acid results, it may be assumed, from the decomposition of the nucleus by means of autolytic enzymes aided perhaps by a special oxydase.

On the other hand, however, the fact has long been known that various tissues are capable of decomposing uric acid. Wiener,[4] Schittenhelm[5] and Almagia[6] have recently studied the question in detail and describe the presence of uricolytic enzymes in various tissues of several animals. Schittenhelm claims that the calf's kidney is most active in this regard with the liver of the same animal second in power. Pfeiffer[7] was able to prove that ninety to ninety-five per cent. of the uric acid added to human kidneys suffered decomposition. In the horse Almagia found the most active enzyme to be in the liver. These results indicate that the liver among other organs possesses the power of forming uric acid by oxidization and perhaps also by synthesis,[8] while at the same time it is capable of decomposing it through the stages of allantoïn and glyoxylic acid.

Austin[9] has raised the point, however, that the alkali in which the uric acid is dissolved is capable of splitting up the latter and that all preparations of uricolytic enzymes contain purin bases which readily become transformed into uric acid. Notwithstanding the latter criticism it seems fairly well founded that the reaction under discussion is a reversible one in which synthetic and analytic processes come into a state of equilibrium in the cell and that alterations in the

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[4] Wiener, H., Ueber Zersetzung und Bildung der Harnsäure im Thierkörper, *Arch. f. exper. Path. u. Pharm.*, 1899, xlii, 375.

[5] Schittenhelm, A., Ueber das uricolytische Ferment, *Zeit. f. physiol. Chem.*, 1905, xlv, 161.

[6] Almagia, M., Zur Lehre vom Harnsäurestoffwechsel, Ueber die Zersetzung der Harnsäure durch die Organe des Saugetheirs, *Beit. z. chem. Phys. u. Path.*, 1905, vii, 459.

[7] Pfeiffer, W., Zur Lehre vom Harnsäurestoffwechsel, Ueber die Zersetzung der Harnsäure durch menschliche Nierengewebe, *Beiträge z. chem. Phys. u. Path.*, 1905, vii, 463.

[8] Burian, R., Ueber die oxydative und die vermeintliche synthetische Bildung von Harnsäure im Rinderleber Auszug, *Zeit. f. physiol. Chem.*, 1905, xliii, 497; Die Herkunft der endogenen Harnpurine bei Mensch und Saugethier, *ibid*, 1905, xliii, 532.

[9] Austin, A. E., The Uricolytic Enzyme in Animal Organs, *Jour. of Med. Research*, 1906, xv, 309. The Uricolytic Enzyme, *ibid.*, 1907, xvi, 7.

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activity of one or the other set of enzymes increase or diminish the elimination of uric acid without the occurrence, necessarily, of an increase or decrease in the amount of purin material formed from the nucleic acid of the nucleus.

If the increased elimination of uric acid in dogs injected with toxic sera is the result of altered uric acid equilibrium of the cell, as just described, one would expect to find that, as more xanthin and hypoxanthin are oxidized to uric acid, less of these purins should be eliminated in the urine. On the other hand, if the uric acid is the result of a new formation from the nucleic acids then an increase in purins also would be expected and at the same time an augmentation in elimination of phosphoric acid in some form[10] as the result of the splitting of the nucleic acid molecule. In the formation of uric acid by the first process no change in phosphoric metabolism should take place.

Methods.—The experiments presented in Tables I, II and III were carried out in the following manner: The animals were placed upon nitrogenous equilibrium after which estimations were made during a three day fore period. An injection was then given, and in two instances a second injection after a lapse of one and three days respectively. The observations were continued until after the maximum effect was reached. The purin-free diet was a casein, cracker dust and lard mixture. The urine was examined for total-nitrogen by the Kjeldahl-Gunning method, the uric acid and purin bases were determined by the Salkowski procedure, and the inorganic phosphates by titration with uranium nitrate, using potassium ferrocyanide as an indicator. The method used for total phosphorus was fusion of the evaporated residue of the urine with sodium hydroxide and potassium nitrate, precipitation with ammonium molybdate in the presence of ammonium nitrate, solution of the ammonio-phosphomolybdate in ammonia and re-precipitation with magnesium mixture. This precipitate was filtered off, incinerated and weighed as magnesium pyrophosphate.

The question of the presence of phosphorus in the urine in organic form has recently received attention from various in-

[10] Jackson, H. C. and Blackfan, K. D., Action of Certain Drugs on the Elimination of Uric Acid During a Nitrogen-free Diet, Albany Medical Annals, 1907, xviii, 24.

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vestigators among whom Bergmann[11] and LeClerc and Cook[12] incline to the opinion that all of the phosphorus of the urine exists in the inorganic form. The latter observers studied the phosphorus content of the urine by means of determinations made by Neumann's[13] method, and by that outlined above, and compared the results with those obtained by the uranium-titration procedure. They show that the results by the dry fusion method are uniformly higher by three to four per cent. than those given either by uranium acetate or by Neumann's method; hence they incline to the view that this difference is within the limits of error and that no organic phosphorus is present in normal urine.

We cannot agree with these conclusions in view of the results obtained by one of us in a study of the elimination of organic phosphorus after the administration of sodium salicylate.[14] Nor do they receive support from the results which are presented in this communication. The constant uniformity of difference shown by the fusion method over that of titration seems to indicate that the difference is not due to the factor of error in the method. We have performed in this connection some preliminary experiments with a view to explaining the differences reported and expect to continue them more in detail. At present we can say that Neumann's method apparently yields results which agree closely with those obtained by titration with uranium nitrate, using potassium ferrocyanide as indicator. When the fusion method is employed the figures obtained are uniformly higher than by both of the other methods. At present, therefore, we incline to the opinion that phosphorus in other than inorganic form is present in normal urine.

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[11] Bergmann, W., Ueber die Ausscheidung der Phosphorsäure beim Fleisch und Pflanzenfresser, *Arch. f. exper. Path. u. Pharm.*, 1901, xlvii, 77.

[12] LeClerc, J. A., and Cook, F. C., Metabolism Experiments with Organic and Inorganic Phosphorus, *Jour. of Biol. Chem.*, 1906, ii, 203.

[13] Neumann, A., Einfache Veraschungsmethode (Säuregemisch-Veraschung), *Zeit. f. physiol. Chem.*, 1902, xxxvii, 115.

[14] Jackson, H. C. and Blackfan, K. D., Action of Certain Drugs on the Elimination of Uric Acid During a Nitrogen-free Diet, ALBANY MEDICAL ANNALS, 1907, xviii, 24.

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TABLE I.

Nuclein Metabolism. Dog 59.

DATE.	Grams Nitrogen as			Grams P_2O_5.		Notes.
	Total.	Uric Acid.	Purin Bases.	Inorganic.	Organic.	
Apr. 10	7.86	0.0015	0.001	0.899	0.147	
11	5.51	0.0159	Lost	0.652	0.093	
12	4.70	0.0141	0.0082	0.690	0.087	
13	4.49	0.0121	0.0097	0.576	0.060	Injection 10 A. M. toxic serum; dose 1: 785.
14	6.97	0.0126	0.0231	1.009	0.085	
15	12.59	0.0246	0.0169	0.690	0.121	Injection 11 A. M. toxic serum; dose 1: 1745.
16	11.08	0.0127	Lost	0.849	0.072	Hburia.
17	13.81	0.0319	0.0287	0.629	0.063	
18	11.93	0.0203	0.0265	0.866	0.023	Killed.

TABLE II.

Nuclein Metabolism. Dog 61.

DATE.	Grams Nitrogen as			Grams P_2O_5.		Notes.
	Total.	Uric Acid.	Purin Bases.	Inorganic.	Organic.	
Apr. 22	3.33	0.0042	0.0086	0.478	0.078	
23	3.53	0.0063	0.0072	0.554	0.052	
24	3.12	0.0050	0.0079	0.584	0.097	Injected 12 M. toxic serum; dose 1:937; vomited.
25	4.57	0.0167	0.0103	0.549	0.085	Hburia.
26	5.74	0.0336	0.0107	0.387	0.074	Hburia.
27	6.83	0.0241	0.0124	0.387	0.084	
28	6.54	0.0200	0.0235	0.326	0.046	
29	5.69	0.0112	0.0086	0.356	0.118	Killed.

TABLE III.

Nuclein Metabolism. Dog 63.

DATE.	Grams Nitrogen as			Grams P_2O_5.		Notes.
	Total.	Uric Acid.	Purin Bases.	Inorganic.	Organic.	
May 14	4.74	0.0057	0.0061	0.520	0.062	
15	4.41	0.0054	0.0068	0.557	0.109	
16	4.26	0.0068	0.0076	0.550	0.072	Injected 11 A. M. toxic serum; dose 1:835; vomited.
17	5.29	0.0249	0.0110	0.641	0.062	
18	4.24	0.0143	0.0068	0.508	0.078	
19	4.34	0.0109	Lost	0.535	0.066	Injected 11 A. M. toxic serum; dose 1:557; vomited.
20	4.75	0.0133	0.0131	0.576	0.066	Hburia.
21	7.64	0.0141	0.0116	0.435	0.090	Hburia.
22	8.38	0.0095	0.0157	0.440	0.075	Hburia.
23	6.21	Lost	0.0133	0.550	0.111	Killed.

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Results.—From the figures in the above table it is evident that the increase of uric acid after injection, as noted in the study of the nitrogenous metabolism,[15] is constant and that there also occurs an increase of purin bases and with one exception of phosphorus pentoxide. This general increase occurs not only after the first but also after subsequent injections. It reaches its maximum on the second day and then falls away. The uric acid increase is greater proportionately than that of the total nitrogen, hence an augmentation of the percentage uric acid in terms of total-nitrogen takes place. The uric acid nitrogen, however, returns to the normal sooner than the latter. The same facts hold true for the purin bases the elimination of which runs parallel, in a general way, to the uric acid output. In the one instance (Table II, Dog 61) in which the phosphorus pentoxide elimination remained constant there still occurred the markedly increased uric acid and purin base output. That the phosphorus pentoxide elimination did not follow that of the uric acid and purin bases is to be explained by the fact that after the injection the animal ate only a quarter of the daily food allowance. Although on the day following the injection the amount ingested of phosphorus pentoxide was therefore diminished, the elimination of inorganic phosphates remained unchanged. This would indicate that an actual increase in endogenous phosphorus pentoxide formation took place, thus bringing the apparent exception in agreement with our other observations. The organic phosphorus elimination was unaltered.

The question as to the cause of the increased output of uric acid during a purin-free diet, observed after various experimental procedures, has been variously explained. Beebe[16] concludes that the increase found after alcohol administration is to be attributed to a diminished oxidative power on the part of the hepatic cells although the purin bases were likewise increased. In commenting upon this view Jackson and Blackfan, from results which they obtained with alcohol, inclined to the opinion that the facts would warrant rather the assumption that the alcohol causes an increased new formation of uric acid and

[15] See third paper of this series "Nitrogenous Metabolism."

[16] Beebe, S. P., The Effect of Alcohol and Alcoholic Fluids upon the Excretion of Uric Acid in Man, *Amer. Jour. of Physiol.*, 1904, xii, 13.

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purin bases, and they adduced as evidence, among other factors, the augmented excretion of organic phosphorus.

According to the view of Schittenhelm, concerning the probable way in which the uric acid is formed from the nucleo-proteid, we would expect, if for any cause oxidation in the hepatic cell is diminished, the xantho-oxydase would be affected, and as a result less uric acid would be formed from the purin bases than under normal circumstances. An increase in purins would also occur if the hydrolytic splitting enzymes were unaffected. An augmentation of uric acid would take place either as the result of a diminished power of the uricolytic enzymes or as the result of an increased new production, other things being equal. In the latter case the purin would also be increased.

The results reported in the paper on nitrogenous metabolism do not indicate that the injection of a hemotoxic serum causes a prolonged or decided decrease in the oxidative power of the hepatic cell. As a whole the organ continues to perform its functions in the normal way. We must therefore explain the increase in purins and uric acid as a decomposition of nuclear material in the autolysis occurring in the areas of necrosis. This is brought about by the hydrolysis of the nucleic acids. Such an explanation agrees with the feeding experiments performed by Sweet and Levene[17] upon a dog with an Eck fistula. They found the ingestion of nucleic acids to be followed by a rise in uric acid and total phosphorus elimination. The fact that the increased excretion of these nuclear compounds usually reaches its maximum in our experiments on the second day, when the autolysis is at its height, would also strengthen this explanation.

The increased elimination of inorganic phosphates which accompanies the output of uric acid would likewise point to the new formation of the latter from the nucleic acids formed as a step in the autolysis of nuclear material. The phosphoric acid radical of these acids is evidently excreted in inorganic form and thus the mechanism differs from that observed in connection with the administration of alcohol and salicylic acid under which circumstances the phosphoric acid is apparently eliminated in organic combination, since no increase in inorganic phosphates occurs.

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[17] Sweet, J. E., and Levene, P. A., Nuclein Metabolism in a Dog with Eck's Fistula, *Jour. of Exper. Med.*, 1907, ix, 229.

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Allatoïn.—In the dog, the largest part of the quantity of uric acid, ingested, as shown by Swain,[18] disappears and is not excreted. In the experiments outlined above it is not improbable, therefore, that a much larger amount of uric acid was produced in the necrosis of the cell nucleus than was eliminated. Of the total amount formed only a small proportion escapes hydrolysis and appears in the urine. Swain also has shown that the ingestion of large amounts of uric acid is followed by the elimination of small quantities of allantoïn.

In order to obtain evidence upon this point the urine of the six animals under observation in the experiments reported in the paper on nitrogenous metabolism, was examined for allantoïn according to the method of Loewi.[19] The results are not uniform but indicate that usually the increase of uric acid is accompanied by an increase in allantoïn; for example, in one the amount of uric acid the day before injection was 0.018 gram and of allantoïn 0.319; in the urine of the twenty-four hour period following the former rose to 0.337 and the latter to 0.669.

CONCLUSIONS.

In necrosis of the liver of the dog produced by hemotoxic immune sera, the increased excretion of uric acid, purin bases and inorganic phosphorus pentoxide is the result of the hydrolysis of nuclear material occurring during the autolysis of the necrotic tissue.

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[18] Swain, R. E., Formation of Allantoin from Uric Acid, *Amer. Jour. of Physiol.*, 1901, vi, 38.

[19] Loewi, O., Beiträge zur Kenntnis des Nucleinstoffwechsels, *Arch. f. exp. Path. u. Pharm.*, 1900, xliv, 20.

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EXPERIMENTAL LIVER NECROSIS. V. THE FATS AND LIPOIDS.[1]

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The results outlined in this communication constitute a partial report of a somewhat comprehensive investigation[2] now in progress of the chemical processes concerned in the variations occurring in the amounts of fats and lipoids in the hepatic cell under normal and various pathological conditions.

It has seemed advisable, in connection with the other investigations of liver necrosis here presented, to discuss at this time only that part of the general study which deals with the fatty changes in hepatic necrosis brought about by the injection of hemotoxic immune serum.

The study of such lesions is of peculiar value in view of the attempts which have been made to bring into a relation of cause and effect the autolysis of the organ and the appearance of the fat. We have, therefore, with this point in view attempted to determine whether in the necrosis (autolysis) which follows the injection of the serum there occurs any alteration in the fat content corresponding to changes observed in the nitrogenous constituents of the cell. Especial interest is attached to this question in view of the somewhat widely divergent opinions held as to the origin of the fat which appears in the so-called fatty transformation of various organs. That the fat does not arise from a peculiar decomposition of the proteid molecule in the cell, the fatty degeneration of Virchow, seems fairly well established. On the other hand, Rosenfeld[3] and others hold that the fat makes

[1] Conducted under grants from the Rockefeller Institute for Medical Research. Published also in *Journal of Experimental Medicine*, 1907, ix, 578.

[2] This investigation, including a study of the fatty changes occurring in various experimental lesions of the liver of the dog and of certain pathological conditions of the human liver, will be published later in full by H. C. Jackson and L. K. Baldauf. We wish to express here our indebtedness to Dr. Baldauf for the privilege of utilizing in this partial report that portion of his work which refers to necroses of the liver produced by hæmotoxic serum.

[3] Rosenfeld, G., Fetbildung, *Ergebnisse der Physiologie*, 1902, i, 651; *ibid.*, 1903, ii, 50.

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its appearance as a simple infiltration from without when for any reason the cell has received an injury which seems to inhibit its oxidizing power. The appearance of fat in organs during phlorhizin poisoning is thus explained by Lusk.[4] Waldvogel,[5] however, who has investigated this question most thoroughly believes that the process is one closely allied to autolysis. His theory is that normally certain substances, which may be called combined fats, such as the ovovitellin of Hoppe-Seyler, or the lecithalbumin of Liebermann, hold the fatty radical in a combination which does not react to microchemical fat stains, such as Scharlach R or Sudan III, and which cannot be removed chemically by the ordinary fat solvents. These substances, however, during autolysis become split in such a manner that the fat radical is liberated in the form of protagon, jecorin, lecithin and even neutral fats. He supports this contention by experiments upon the livers of phosphorus-poisoned animals and upon normal livers undergoing autolysis, in which he has shown there is a marked augmentation during autolysis of such substances as protagon, jecorin, cholesterin, fatty acids and neutral fats. The lecithin, on the other hand, is diminished.

Siegert[6] has also shown that, although in autolysis the ether extract of the liver does not increase, a marked rearrangement of the fatty compounds of the extract takes place, and that the jecorin rapidly suffers decomposition. This is not in accord with Waldvogel's results. In this connection it may be mentioned that Taylor[7] has conducted experiments upon normal and phosphorus-poisoned frogs and finds that, although the absolute amount of free fat may not increase after the administration of phosphorus the combined fats estimated after digestion with pepsin-hydrochloric-acid suffer a marked diminution equivalent to two-thirds of the amount originally present.

As stated in previous papers in this series phosphorus poisoning does not seem to set up in the liver processes which are

[4] Ray, W. E., McDermott, T. S. and Lusk, G., On Metabolism During a Combination of Phosphorus Poisoning and Phlorhizin Diabetes, *Amer. Jour. of Physiol.*, 1900, iii, 139.

[5] Waldvogel, Autolyse und fettige Degeneration, *Virchow's Arch.* 1904, clxxvii, 1. Phosphorvergiftung und Autolyse, *Deut. Arch. f. klin. Med.*, 1905, lxxxii, 437. Waldvogel and Mette, Die Autolyse in Menschlichen fettige degenerierten Organen, *Münch. med. Woch.*, 1906, ix, 402. Waldvogel, Die durch Fermente bewirkten Umwandlungen bei der fettigen Degeneration, *Zeit. f. physiol. Chem.*, 1904, xlii, 200.

[6] Siegert, F., Das Verhalten des Fettes bei der Autolyse der Leber, *Beiträge zur chem. Physiol. u. Path.*, 1902, i, 114.

[7] Taylor, A. E., On Fatty Degeneration, *Jour. of Med. Research*, 1903, ix, 59.

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strictly analogous to autolysis following necrosis, hence the results to be presented must not be considered as strictly comparable to those obtained in other lesions.

Few attempts have been made to study the effect of a true necrosis upon the fat constituents of the cell. Dietrich,[8] as the result of histological studies, claims that autolysis is not an important factor, since tissues introduced into the peritoneal cavity in collodion sacs do not show fatty change. When the tissue, however, is not enclosed in sacs, fat droplets appear which are present not in the cell substance but in the interstices of the tissue. He also tied off the renal arteries and found a "deposition" of fat around the necrotic areas. He believes, therefore, that fat will not appear if the cell is completely dead as in necrosis; but only when it continues to functionate incompletely, as, for example, must be the case with the cells around necrotic areas.

This opinion we can confirm as the result of the histological study of focal necrosis caused by hemotoxic serum. Frozen sections of formalin-hardened material stained with Scharlach R never show more fat, and usually less, than the surrounding adjacent normal liver tissue. There is always present however, in lesions twenty-four to forty-eight hours old a very definite and striking accumulation of fat in the ring of more or less degenerated cells lying between the necrotic and normal liver. These cells correspond to those which in hematoxylin and eosin preparations present a vacuolated, granular protoplasm and pycnotic, poorly staining, nuclei.[9]

Di Cristina,[10] who conducted experiments somewhat after the nature of those of Dietrich, and made chemical analyses by Rosenfeld's method, states that no increase of fat occurs in the necrosis caused by shutting off completely the renal circulation. Of considerable interest in connection with Dietrich's view are the experiments reported by Bainbridge and Leathes.[11] These investigators ligated the hepatic artery alone and thereby obtained an increase in fat but no necrosis.

[8] Dietrich, A., Experimente zur Frage der fettigen Degeneration, *Münch, med. Woch.*, 1904, li, 1510.

[9] Pearce, R. M., Regenerative Changes in the Liver: A Study of Experimental Lesions in the Dog, *Jour. of Med. Research*, 1906, xv, 99.

[10] Di Cristina, Die chemischen Veränderungen bei fer fettigen Degeneration in Beziehung zur den anatomischen, *Virchow's Arch.*, 1905. clxxxi, 509.

[11] Bainbridge, F. A. and Leathes, J. B., The Effect of Arterial or Venous Obstruction upon the Nutrition of the Liver Cells, *Biochem. Jour.*, 1906, ii, 25.

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The ligation of the portal vein on the other hand resulted in atrophy of the cells and some necrosis, but no augmentation of fat. These experiments appear to confirm the idea that the cells must retain in part their normal function and be normally bathed with the circulating fluids in order to give rise to the appearance of fat within them.

In concluding this brief discussion which merely suffices to indicate the trend of opinion in regard to the subject under investigation it may be said that much of the discrepancy in the results reported can be safely ascribed to the varying methods employed especially in connection with the extraction of the fatty material from the tissue. Siegert has also emphasized the ease with which the extracted products undergo laboratory changes.

Methods.—The organs were removed from the body quickly, put through a hashing machine, weighed, and dried under absolute alcohol at about 70–80° C. At this stage the partially dry material was weighed and then ground in a machine to an impalpable powder. Part of this was further dried in a desiccator to constant weight and upon this was calculated the dry substance and nitrogen content of the original tissue. Another weighed part was extracted in a Soxhlet with alcohol and chloroform successively according to the method of Rosenfeld. Each total extraction with alcohol and with chloroform lasted on an average thirty hours. In some cases the original partly-dried material was so fatty that a rough extraction with chloroform at room temperature preceded the grinding. This extract was added to the subsequent one obtained from the Soxhlet. The total fat was taken up in a definite volume of chloroform. An aliquot portion of this was evaporated to complete dryness at about 70° C. and from this was calculated the fat per cent. of the tissue.[12]

For our purposes it was not thought necessary to keep separate for analysis the alcohol and chloroform extracts as Waldvogel does with alcohol and ether. This procedure is exceedingly time consuming and we have employed another and simpler method which we believe has given results

[12] We have employed chloroform in this connection, since, in the first place, it is a much readier solvent for the fatty compounds than either sulphuric or petroleum ether, and secondly, because all of the ether we could obtain reacted distinctly acid to phenolphthalein, a fact already alluded to by Baldauf, Chemistry of Atheroma and Calcification (Aorta), *Jour. of Med. Research*, 1906, xv, 355.

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equally definite. Instead of attempting to decide whether the fat compounds present in the extract underwent any change or rearrangement, such as is described by Waldvogel during autolysis of normal tissues and in phosphorus poisoning, it seemed sufficient to determine the nitrogen and phosphorus pentoxide content of the extract, and from these figures to calculate the relationship of the nitrogen to the phosphorus. Since the molecule of the lecithins contains one nitrogen and one phosphorus atom the relationship P:N= 1:1; in jecorin, however, this ratio is 1:4 and in protagon about the same, varying from 1:3.4 to 4.8. The latter figure is calculated from the analyses of Dunham.[13] It is seen, therefore, that the greater the preponderance of substances of the jecorin and protagon type in the extract the higher would be the P:N ratio. On the other hand, if these substances should undergo an autolytic change whereby lecithin and fatty acids were produced, this ratio should fall to the neighborhood of 1:1. Hence from variations in this ratio, changes in the fatty constitutents of the extract should be readily determined.

Measured portions of the chloroform extract were analyzed in duplicate as follows:[14]

Total nitrogen by the Kjeldahl-Gunning method; phosphorus pentoxide by the usual fusion procedure and weighing as magnesium pyrophosphate and the iodine equivalent as outlined by the Association of Official Agricultural Chemists.[15] With some exceptions portions of the tissues analyzed were stained with hemotoxylin and with Scharlach R for the purpose of determining roughly in a comparative way the extent of the necrotic lesion and the fat content.

Results.—The table presents the results obtained in the analysis of four dog livers with normal, four to five, per cent. fat content, one apparently normal but very fatty liver with 21.9 per cent., five with focal necrosis and three with diffuse necrosis of varying degree. As can be seen no relation exists between the degree of necrosis and the amount of fat present. The high amount of fatty material which is present in the

[13] Dunham, E. K., Further Observations on the Phosphorized Fats in Extracts of the Kidney, *Proc. of Soc. for Exper. Biol. and Med.*, 1905, ii, 63.

[14] In most instances the chloroform had to be *completely* removed before the commencement of the analysis.

[15] U. S. Dept. of Agriculture, 1899, *Bulletin* 46, 50.

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TABLE I.

Fats and Lipoids.

Experiment.	Tissue. PER CENT. Dry Substance.	Dry Substance Fat-free.	Fat. Moist Substance.	Fat. Dry Substance.	Nitrogen. Dry Substance.	Nitrogen. Dry Substance. Fat-free.	Alcohol-Chloroform Extract. PER CENT. Nitrogen.	P_2O_5.	P:N	Iodine Equivalent.	Fat by Scharlach R.	Lesion.
1	25.6	22.6	3.97	15.5	12.7	15.0	—	—	—	58.3	+	Normal.
5	28.6	24.1	4.55	15.9	9.7	11.5	1.8	2.6	1:7.0	60.0	?	Normal.
2	24.5	19.5	4.95	20.2	12.7	15.9	2.5	5.2	1:4.9	56.6	+	Normal.
4	18.5	13.7	4.75	25.7	9.2	11.3	1.5	3.6	1:4.4	53.4	+	Normal.
18	40.7	18.8	21.85	53.7	7.5	12.6	0.6	1.3	1:4.5	47.0	+ + +	Normal (very fatty).
7	29.8	26.7	3.10	10.4	9.3	13.2	3.1	7.3	1:4.3	67.7	?	Focal necroses.
6	25.3	21.2	4.12	16.3	12.5	16.7	2.4	7.0	1:3.5	58.3	?	Focal necroses.
26	28.3	24.5	3.84	13.6	9.9	13.8	2.1	5.0	1:4.3	58.7	+	Extentive focal necroses.
43	41.1	24.9	16.23	39.5	8.3	14.0	0.7	2.0	1:3.8	47.0	+ +	Extensive focal necroses.
27	26.0	20.3	5.72	22.0	11.5	15.5	1.5	6.5	1:2.4	49.3	+ +	Extensive focal necroses.
21	41.1	14.9	25.15	61.2	6.7	10.5	0.3	1.1	1:3.0	50.0	+ + +	Diffuse necrosis.
28	23.2	18.8	4.43	19.1	11.9	15.5	2.3	5.8	1:4.3	50.3	+	Diffuse necrosis.
29	21.9	20.1	4.88	19.5	12.7	16.3	2.3	6.1	1:4.0	62.3	+	Diffuse necrosis (most marked).

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normal liver, extractable by the newer method of Rosenfeld, is at first glance surprising, but is in accord with the results of recent investigators. The fat per cent. of all the necrotic livers falls between the normal limits with the exception of 43 and 21 which are above the normal, but these do not represent the most extensive necrosis. Experiments 28 and 29, with the most diffuse necrosis, show normal amounts of fat.

The point which was emphasized in one of the previous papers[16] concerning the percentage of dry substance in the fatty livers is well shown in the table. Whenever the fat per cent. rose above normal the per cent. of dry substance rose almost proportionately. This relation is readily seen by referring to that column in the table in which is given the per cent. of fat-free dry substance. With two exceptions, the dry substance without fat falls between 18.8 to 26.7 per cent. and this surprisingly small variation is in no definite relation to the amount of fat present. The two exceptions are one with normal and one with high fat content. Waldvogel has claimed that as the fatty autolysis increases the water content of the tissue also rises. We would be inclined to ascribe this rather to the nitrogenous autolysis *in vivo* which as we have pointed out elsewhere[16] tends to diminish the amount of dry substance if the circulation is not too greatly impaired. This is shown clearly in Experiments 27, 21, 28 and 29, with the most pronounced necrosis, in which it is seen that the figures for the dry fat-free substance lie on the lower edge of the variation limit for this factor.

As regards the nitrogen content of the tissues a somewhat similar condition of affairs is evident, and although this point does not come directly into this part of the general subject it is of considerable interest. It will be seen that the per cent. nitrogen of the fat-containing dry substance varies within rather wide limits (6.7 to 12.7 per cent.). In those instances, however, where the fat content is high the nitrogen per cent. is low, as would be expected. If, however, the nitrogen of the fat-free dry substance is considered, it is found that the figures for this factor are surprisingly constant throughout (10.5 to 16.7 per cent.). Some of the lowest and

[16] See first paper of this series, "The Hexon Bases."

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highest values occur where, as regards the fat content, the liver tissue was perfectly normal. This indicates apparently that in conditions such as those under discussion, when an increase in fat-content occurs, the material which is represented by the nitrogen of the tissues, suffers no decrease or increase in amount. If then the fat originates from some compound proteid antecedent, the proteid component remains apparently unchanged.

A consideration of the character of the fatty extract obtained from normal and necrotic tissues presents some interesting facts. In regard to the iodine equivalent, which indicates roughly the content of oleic acid in the fat mixture, it is evident that as the fat per cent. increases the iodine absorption factor falls below normal (Experiments 18, 43, 27 and 21). This low iodine factor associated with increased fat content would of course point to a diminishing content of oleic acid radicals as the fat is heaped up in the cell. This again directly opposed to the finding of Waldvogel in phosphorus poisoning.

An examination of the nitrogen and phosphorus pentoxide percentage of the fatty extracts indicates that somewhat wide variations are present, the nitrogen varying from 0.3 to 3.1 and the phosphorus pentoxide from 1.1 to 7.3. It is evident, however, that the lower percentages are in those experiments in which the greatest amount of fat is present (Experiments 18, 43, 27 and 21). With these exceptions the percentage figures are quite regular. Only one explanation can be made of this difference. That is, that as fatty compounds make their appearance in the cell, those substances predominate which do not contain nitrogen or phosphorus, namely the neutral fats, fatty acids and cholesterin.[17]

Of particular interest is the ratio of phosphorus to nitrogen discussed above. It is seen from an examination of the figures in the table that this ratio remains remarkably constant regardless of the absolute variation in the figures. The ratio, with the exception of Experiment 5 which is high, varies only from 1:2.4 to 4.9. If we also exclude Experiments 21 and 27 the variation is still further reduced to 1:3.5 to 4.9,

[17] We possess confirmatory evidence upon this point in the results which have been obtained with the saponification equivalent. These will be published in a later paper.

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which is well within the limits of error or better perhaps within the calculation error as made from the published figures for nitrogen and phosphorus percentages of such poorly defined substances as protagon and jecorin. This high ratio indicates that the nitrogen- and phosphorus-containing fats present in the extracts are of the protagon and jecorin type and remain so irrespective of the amount of fat appearing in the cell.

It must be admitted that some slight evidence does exist to indicate that perhaps under certain conditions these bodies may undergo autolysis. In the two experiments, for example 21 and 27 with a low ratio (1:2.4 to 3.0), considerable autolysis must have been going on during the extensive necrosis and the low ratio as a concomitant factor would point to the appearance in the extract of bodies such as the lecithins, which as previously stated possess a ratio of 1:1. In these experiments roughly one-third of the nitrogen- and phosphorus-containing fats has been replaced by lecithin, according to this reasoning. We are somewhat sceptical, however, of the validity of this line of argument since it does not agree with Waldvogel's observations; nor is the low ratio present in the two experiments (28 and 29) where one would expect it to be most markedly diminished since the necrosis was most pronounced. In these two instances, however, the ratio is normal. As the low ratio occurs in only two out of the eight experiments in which necrosis was present, we are more inclined to believe that some other factor is the true cause for the change.

SUMMARY.

1. Changes which occur in the fat content of the liver of dogs receiving hemotoxic serum bear no relation to the degree of necrosis produced by this serum.

2. An increase in water content of the tissue seldom occurs, but where present is due to the nitrogenous autolysis rather than to the deposition of fat.

3. The appearance of fat in the cell is not associated with a decomposition of the proteid component of the compound fats, but rather to a simple splitting off of the fatty radical. This is shown by the slight variations occurring in the percentage nitrogen of the fat-free substance.

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4. The iodine equivalent diminishes as the fat content increases. This would indicate that in the fatty changes which occur, fats other than those containing oleate radicals make their appearance.

5. The ratio of phosphorus to nitrogen in the alcohol-chloroform extract remains practically constant in all degrees of necrosis. Hence the substances of the protagon and jecorin type hold the same relation to the lecithins during the autolysis as they do normally.

6. In a general way it may be said that the results obtained in the microchemical staining of the fats with Scharlach R agree with those found by chemical extraction methods.

AN INVESTIGATION OF THE NATURE OF PROTEID-SOAP COMPOUNDS AND OF THE STAINING OF PURE FATS AND LIPOIDS BY SCHARLACH R AND SUDAN III.*

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These studies were undertaken for the purpose of further investigating certain reactions on which Klotz[1] bases in a large part his interpretation of pathologic calcification and which, as his interpretation is not in accord with that reached by Wells[2] and independently by me,[3] are matters of considerable importance in the elucidation of this interesting problem.

The observations in question are those concerning the value of the so-called proteid-soap compounds and of the staining of fats and lipoids by Sudan III and Scharlach R.

PROTEID-SOAP COMPOUNDS.

Klotz, as the result of a series of microchemical examinations of various kinds of calcified tissues, concluded that the deposi-

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* This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association. Published also in *Journal of the American Medical Association*, 1907, xlix, 642.

[1] Studies on Calcareous Degeneration, I. The Process of Pathological Calcification, *Jour. Exp. Med.*, 1905, vii, 633.

[2] Pathologic Calcification, *Jour. Med. Research*, 1906, xiv, 491.

[3] Chemistry of Atheroma and Calcification (Aorta), *Jour. Med. Research*, 1906, xv, 355.

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tion of lime in tissues undergoing calcareous degeneration is dependent on the formation of calcium soaps as an intermediate step. He further states that an essential factor in the production of these soaps is the initial combination of a soluble soap and an albuminous substance. He does not assume, however, that this is the essential process in all varieties of pathologic calcification, but states that in exceptional cases there may be two other possibilities: First, "that under certain conditions the calcium salts act directly on the neutral fats present in the degenerating cells," or, second, "that the neutral fats are first broken down into fatty acids and that these react with the calcium salts to form the soaps."

As he was convinced that the combination of soaps with proteid is a necessary intermediate product in certain forms of calcareous degeneration, he attempted to reproduce the reaction in the test tube. To a weak solution of a soap (sodium stearate, oleate or palmitate), a dilute solution of egg albumen was added. In a half hour or longer, at room temperature, a white flocculent precipitate appeared. This he considered to be a combination of the soap and the egg albumen. When this product was treated with Sudan III the same pinkish color, visible in the "soap" granules in tissues undergoing calcification, was seen to be present. The amount of precipitate, he states, is further increased by the passage of carbon dioxid (CO_2) through the solution. Acid calcium phosphate, which does not affect simple solutions of egg albumen, when added to a mixture of egg albumen and soap causes a rapid and dense precipitation.

As microchemical reactions in tissues are notoriously unreliable and controlled only with great difficulty, these reactions in the test tube necessarily formed the basis of Klotz's theory and their explanation is, therefore, of the greatest importance.

The first step in the present investigation was to determine the nature of this precipitate, that is, whether a real combination of proteid and soap does occur, and if not, to ascertain the actual composition of the precipitate. These experiments were carried out with egg albumen and the blood serum of horses. The soluble soaps used were sodium stearate and sodium oleate. In repeating the experiments of Klotz an identical reaction was obtained, that is, on the addition of the soap solutions to the egg albumen or horse serum a flocculent precipitate appeared which

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gradually increased in amount and reached its maximum at the end of twenty-four hours. In order to determine whether or not this was the result of a true combination of proteid and soap or merely a precipitation of some substance in the mixture, the following experiment was performed: Two lots of 100 cubic centimeters each of horse serum were taken; to one, 100 cubic centimeters of distilled water were added, and to the other 100 cubic centimeters of freshly-prepared five per cent. sodium oleate solution. At the end of twenty-four hours a finely granular precipitate was visible in the serum-water mixture, while in the serum-soap solution a copious flocculent precipitate appeared. These were filtered and yielded clear straw-colored filtrates. In order to determine whether or not any combination of proteid had taken place in the soap-proteid mixture, duplicate total nitrogen determinations were made, by the Kjeldahl method, on aliquot parts (five cubic centimeters) of each of the filtrates. The results were as follows:

TOTAL NITROGEN.

SERUM AND WATER MIXTURE.	SERUM AND SOAP MIXTURE.
20.15 c.c. of $\frac{N}{10}$ acid.	20.15 *c.c. of* $\frac{N}{10}$ *acid.*

From these figures it is easily seen that the nitrogen (proteid) contents of both filtrates was the same and that no more nitrogen was thrown out of solution by the soap than by the water alone. This finding is of considerable importance, for if a true combination of proteid and soap had taken place the filtrate obtained after the removal of the precipitate would have contained less nitrogen (an indication of soluble proteid) than the filtrate from the serum-water mixture, where no combination was suspected. As this did not occur the conclusion is inevitable that the precipitate is not a proteid-soap compound, but must consist of a mixture of other substances thrown out of solution.

In order to throw more light on this reaction, experiments were made to determine the influence of the colloids (globulins, albumins) and salts of the serum and egg albumen in the precipitation of the soaps.

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GLOBULINS.

The fact that Klotz emphasized the increased precipitation after the passing of carbon dioxid through the fluid suggested the possibility of the globulins of the serum being the main constituent of this precipitated material. It is a well-known fact that globulins are precipitable from neutral solution on addition of carbon dioxid gas. Globulins, therefore, were prepared from normal horse serum in the usual way (ammonium sulphate method with dialysis). The globulin thus obtained was dissolved in a ten per cent. solution of sodium chlorid and a small quantity of it added to a weak solution of sodium stearate. Immediately a heavy flocculent precipitate appeared. As a control, however, a ten per cent. solution of sodium chlorid was added to a solution of the soap, and an apparently identical precipitation occurred.

It was evident, therefore, that the material precipitated in the first instance was not the globulin but the soap. This reaction is analogous to the salting out of soaps in their commercial manufacture. In an attempt to exclude this factor the globulin was put in solution with the smallest possible quantity of salt, but in every case control experiments using solutions of the same strength of sodium chlorid showed an equal and similar precipitation. The only part then which the globulin can play in this precipitation lies in the reaction noted above in which the globulin of the serum or of the egg albumen can be precipitated by the addition of water alone.

INORGANIC SALTS OF THE BLOOD SERUM AND EGG ALBUMEN.

To a weak solution of sodium stearate, an equal quantity of physiologic sodium chlorid solution was added. As control, an equal quantity of distilled water was added to another portion of the sodium stearate solution. At the end of twenty-four hours a precipitate was visible in both tubes, but was more marked, however, in the sodium chlorid solution. In the sodium stearate and water mixture the precipitate was finely granular and to a certain extent, diffuse, while in the soap-sodium chlorid mixture it was more flocculent and the supernatant fluid slightly translucent.

As a further control, a solution of the normal salts of the serum were obtained as follows: One hundred cubic centimeters

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of horse serum were added to 400 cubic centimeters of distilled water. The mixture was then boiled and the proteid coagulated by the careful addition of acetic acid. The filtrate, clear and colorless, was then evaporated to dryness to remove the excess of acetic acid and by the addition of distilled water was brought up to the original volume of the serum. A similar solution of salts of egg albumen was obtained after removal of the coagulable proteids. To ten cubic centimeters of each of the proteid-free solutions ten cubic centimeters of sodium stearate solution were added. At the end of twenty-four hours a precipitate was visible which, although much finer in appearance, approximately corresponded to the precipitate formed by the addition of the physiologic sodium chlorid solution to the sodium stearate. As the result of these tests it may be stated that while the inorganic salt content of egg albumen or of serum does not probably cause the whole of the voluminous precipitate obtained on addition of soap to the proteid, it is a factor in the production of a small amount of it.

In this connection attention must be called to the calcium content of the egg albumen (1.7 to 2.9 per cent. of the ash) and blood serum (.015 per cent. of the serum). In both of the reactions with these fluids and the soaps this calcium is undoubtedly a factor in precipitating this latter as calcium compounds.

ALBUMINS.

The effect of salt-free albumins was then investigated. These were prepared by dialyzing egg albumen and horse serum for about ten days or until tests for chlorids were negative. In each instance the precipitated globulins were filtered off; in the case of the serum a small amount of water soluble globulin probably still remained in solution. Comparing solutions of albumins so prepared plus stearate soaps with the control solutions of egg albumin and serum albumin respectively in water, at the end of twenty-four hours no difference was visible. In all the tubes a very small amount of a very finely granular precipitate occurred.

These reactions render it probable that the albumins do not enter into the composition of the precipitate which is formed when the soaps react with the egg albumen. In order, however, to exclude the possible factor of the albumen inducing a "colloidal precipitation" experiments were performed with other

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colloid substances, for instance, gelatin and starch. With gelatin a marked precipitation was apparent with the soaps, but as the admixture of calcium salts with this substance could not be eliminated, solutions of other colloids like starch were tried.

A rather fluid starch paste was prepared. Some of this was added to equal parts of egg albumen and blood serum. In both cases a somewhat gelatinous precipitate occurred which was shown to consist of starch. Solutions of starch added to the soap solutions caused a precipitate which was analogous to that produced by water alone. Apparently, therefore, colloids may precipitate starch from solutions as well as soaps, but the reverse does not occur.

Thus far only a small amount of the precipitate has been accounted for. We have shown that the inorganic salts of the serum are responsible to a slight extent in the precipitation of the soaps; the albumins on account of their colloidal nature, possibly also in the same degree, while the globulins enter only slightly into the composition of the precipitate as a result of the dilution of the mixture by the solutions added.

FATTY ACIDS.

The changes occurring in soap solutions suggested the possibility of fatty acids playing a part in the precipitate. For example, a weak solution of sodium stearate or oleate freshly prepared and filtered is translucent and free from any precipitate. When tested with litmus it is alkaline in reaction. If it is allowed to stand for twenty-four hours a granular precipitate in the case of the stearate, gelatinous in the case of oleate, gradually appears.

If the precipitates are filtered off and the filtrates allowed to stand for twenty-four hours a similar precipitate reappears. This precipitate is insoluble in water, but dissolves readily in ether and chloroform. Such a chloroform solution reacts acid to litmus and contains fatty acid. These facts just outlined can be easily explained. Part of the soap on passing into solution undergoes dissociation and hydrolysis with the production of sodium hydroxid (NaOH) and free fatty acid. The mixture, therefore becomes alkaline and the fatty acids gradually precipitates. This passes into solution in the chloroform.

With these changes in mind, the proteid-soap compounds were

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examined as follows: A quantity of the precipitate obtained on the addition of a sodium oleate solution to egg albumen in suspension was now shaken up with the neutral chloroform and found to a great extent to be soluble. Tested with litmus, the chloroform reacted acid to litmus and the neutral point was only reached after the addition of a definite amount of a deci-normal solution of sodium hydroxid. This observation, therefore, demonstrates conclusively that the major portion of the precipitate which Klotz considers to be a proteid-soap compound is composed of fatty acids.

Fatty acids may also be thrown out of solution on the addition of weak acids. If carbon dioxid (CO_2), which in aqueous solutions is a weak acid, be passed through a solution of soap, a flocculent precipitate gradually separates out, which when taken up in chloroform and tested, reacts acid to litmus. In the formation of the hypothetical proteid-soap compound Klotz emphasized this increased precipitation on the addition of carbon dioxid. He further states that the precipitation is increased by the addition of a solution of acid calcium phosphate. This reaction is, of course, due in part to the precipitation of the fatty acids by the acid solution and also to the formation of insoluble calcium soaps by the addition of a soluble calcium salt.

To summarize briefly: The so-called proteid-soap compound does not exist. The material may be due in small part to a precipitation of the soaps by the inorganic salts of the serum or egg albumen and in small part to globulins thrown out of solution. An equally small part is caused by a precipitation of the soaps or fatty acids by the colloid substances in the serum and egg albumen. The main portion of the precipitate, however, consists of fatty acids obtained from a hydrolysis taking place in the soap solutions.

THE STAINING OF FATTY COMPOUNDS WITH SUDAN III AND SCHARLACH R.

Klotz states that the soaps are ready solvents for Sudan III. He attempts to demonstrate this by making a concentrated aqueous solution of the soap and adding powdered Sudan III. He states that the clear, deep, red solution which results can be filtered, diluted and, when evaporated to dryness, yields pinkish yellow areas which are distinguishable from the golden-red stain-

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ing fat. He cites the statement of Fischler, who asserts that Sudan III is soluble in soap solutions, but who further states, however, that the soap when stained with Sudan III rapidly loses its color when treated with 70 per cent. alcohol, the color being transferred to the alcohol. With this latter statement Klotz fails to concur wholly. He admits that this is true in regard to soap solutions in the test tubes, but states that soaps in the tissue are less soluble in weak alcohols. The retention of the stain here, he thinks, is due to the combination of the soaps and proteids already discussed. These observations, in view of our experience with the proteid-soap compounds, demand re-investigation.

Scharlach R and Sudan III are soluble in alcohol, chloroform, ether, toluol, acetone, etc., and in certain fats and lipoids. When added to water no color is imparted to the fluid even at the end of several days. It is generally accepted that the stains are insoluble in water.

SOLUBLE SOAPS.

If to a fairly concentrated solution of sodium oleate which has been freshly made and filtered a small quantity of Sudan III is added, after "thorough mixing," no color is immediately imparted to the fluid. Gradually, however, the solution assumes a pinkish color which, after standing for a while, becomes much deeper. At the end of twenty-four hours the solution is colored a deep red. If some of this solution is shaken with ether or chloroform the color immediately leaves the aqueous solution and is transferred to the chloroform and ether. When tested with litmus the solution reacts strongly acid, and if evaporated to dryness, reddish yellow granules of fatty acid are visible under the microscope.

The colorless condition of the soap solutions immediately after the addition of the Sudan III and the gradual reddening of the mixture must be attributed to the same reaction previously described where the soaps slowly undergo hydrolysis and the fatty acids formed thereby gradually assume the stain which eventually colors the solution a deep red. In other words the deep orange red color is not due to the soaps which have taken up the stains, but rather to the fatty acids formed by hydrolysis and temporarily held in solution by the soaps.

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CALCIUM SOAPS.

To a quantity of the original reddened aqueous solution of the soluble soap a quantity of absolute alcohol was added sufficient to raise it to a seventy per cent. alcohol solution. When this alcoholic solution was treated with a soluble calcium salt, a pinkish white precipitate appeared at the end of twenty-four hours, the supernatant fluid remaining deep orange red. The precipitated substance was filtered off; when dried it appears white and very fluffy in consistence. It is insoluble in water, but dissolves in chloroform when a few drops of a mineral acid are added. The precipitate is, therefore, calcium soap which does not take the stain with Sudan III.

In order to prove this point more decisively attempts to stain calcium soaps were made in another manner. Calcium soaps were prepared by the precipitation of the soluble soaps—sodium stearate and oleate—with a soluble salt of calcium. The collected precipitate was thoroughly washed with water to remove soluble salts and afterward with alcohol to remove traces of fatty acids. In the case of the stearate a finely granular opaque white salt was obtained, while with the oleate compound a rather gelatinous material resulted.

A relatively large quantity of the insoluble calcium stearate was suspended in an absolute alcohol solution of Sudan III. As has been previously shown, calcium soaps are rather insoluble in cold absolute alcohol. The suspended material, now filtered off, appears pinkish white. Washed with absolute alcohol, the pinkish color disappears and is imparted to the wash alcohol. The insoluble soap remains opaque white. The pinkish color of the soaps treated with Sudan III is not due to real staining, but is produced by a mere mechanical mixture of the dissolved stain and the insoluble compounds. Attempts which were made to stain these soaps by methods outlined below were also fruitless.

NEUTRAL FATS AND LIPOIDS.

It was deemed extremely important to determine if Scharlach R and Sudan III could be used as differential stains for the various fats and lipoids. Several methods of demonstrating this were tried. For example, the examination of frozen sections of colloids (gelatin, celloidin) and of various fresh and dehydrated animal tissues impregnated with solutions of the fat and

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lipoids to be examined. These methods were abandoned in favor of the following, which seemed to be more applicable to the problem:

To solutions of fat and lipoids Scharlach R and Sudan III respectively were added. The resultant clear solution was thrown into water and the fats precipitated out of their original solution. This method we considered relatively successful because of the ease with which the stained fat can be separated from the solvent. While the fats are fairly soluble in alcohol and ether, they dissolve much more readily in chloroform, which is also an excellent solvent for Sudan III and Scharlach R. Chloroform also will not mix with water, that is, it is insoluble in that liquid.

If, therefore, a chloroform-Sudan III solution of a fat is added to water the fat will precipitate out, so will the chloroform and although both may be colored red, the fat rises to the surface of the fluid while the chloroform settles to the bottom, allowing an easy differentiation. The chloroform, however, must be removed by evaporation with heat before one may say definitely that the red globules are the fatty compound and not the chloroform. In this method a portion of stain remains adherent to the floating fat, while most of the insoluble stain is suspended through the fluid. It is necessary, therefore, that this fat be not filtered, but skimmed off, redissolved in the solvent and reprecipitated several times in order to be certain that the red color is due to the fat alone and not to any of the insoluble stain which may have been accidentally caught in the suspension. This method, although a cumbersome one, has been found most excellent for determining the staining power of various fats and lipoids. The same method may be used when alcohol is employed as a solvent.

In his original communication Klotz expresses a preference for Sudan III, for while he found that Scharlach R stained more intensely, staining with Sudan III was more satisfactory in that the precipitation of crystals from the saturated solution was more easily obviated. In the method which I adopted this difficulty was not encountered. Scharlach R and Sudan III were used interchangeably. No differences were noticeable in fats and lipoids stained with either Scharlach R or Sudan III except differences which would distinguish the original alcohol solutions. Scharlach R stains fats more intensely, the red being much deeper and more pronounced. Fats stained with Sudan III assume more of a deep orange-red color. The staining of fats by these dyes is

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dependent on the fact that these dyes are more soluble in the fats than in the solution in which they are originally dissolved.

FATTY ACIDS.

Pure oleic, palmitic and stearic acids were employed in the following experiments:

Oleic Acid.—To a definite quantity of oleic acid a small amount of Sudan III in substance was added; solution occurred immediately and the liquid oleic acid was colored a deep red. This color was much more intense than that of the saturated seventy per cent. alcoholic solution. When the oleic acid was filtered into distilled water it separated as deep red opaque globules. Repeated solution and reprecipitation failed to cause the acid to lose its deep red color.

Palmitis Acid.—The acid was dissolved in absolute alcohol and Sudan III added. The solution was now filtered into distilled water. The acid thrown out of solution was not nearly so deeply tinted as the oleic acid and appeared light red in color. If the fluid on which this reddish fatty acid material was floating is heated to about the boiling point the fatty acid melts into globules which take on an intensely red color exactly similar to that obtained when the stain was dissolved in the oleic acid. On cooling the acid separated out as firm red globules. This material collected and redissolved in absolute alcohol was filtered again into distilled water. The fatty acid which now separated out appeared almost white, the slight pinkish color being due to the color of the fluid in which it was suspended. If, however, pure palmitic acid is heated to its melting point and a few particles of the Sudan III are added the acid dissolves the stain and the fluid takes on the deep red color which was noticed in the case of the oleic acid.

Stearic Acid.—The same results were obtained with this acid.

CHOLESTERIN.

This substance obtained in pure form from gallstones was treated by the same method. The first precipitate appeared deep red, but further solution and re-precipitation removed all the color until the final material was almost a pure white. If cholesterin is raised to its melting point and Sudan III in substance is added the fluid cholesterin dissolves the stain and takes

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on the same deep red color noticed with the oleic acid and fluid palmitic acid. This indicates that only when cholesterin is in a fluid state will it take the stain.

NEUTRAL FATS.

Neutral fats were obtained from both mutton and beef suet. Treated in a manner similar to the other fats, the neutral fluid or semi-fluid fats retained their deep red color after repeated precipitations.

LECITHINS.

Lecithins were prepared from the yolks of eggs and from brains dehydrated with dried calcium sulphate. A quantity of egg lecithin dissolved in a chloroform solution of Sudan III was added to water. The deeply red-colored chloroform fell to the bottom of the vessel. On removal of the chloroform by heat over a water bath, the stain came out of solution and suspended itself in the fluid; the lecithin, on the other hand, assumed a swollen pasty condition like a stiff emulsion which retained a distinct salmon-yellow color. This gelatinous material, which could be lifted out of the solution on a stirring rod, was transferred to fresh amount of distilled water, in which it then dissolved, coloring the aqueous fluid a light yellow pink.[4] This indicates that lecithin in solution has the power to stain feebly.

In a second experiment with lecithin a quantity of a chloroform solution obtained from dehydrated brain was added to Sudan III solution. The filtered solution was allowed to evaporate spontaneously and the residue examined under the microscope. Everywhere orange-red globules (lecithin) were interspersed among a yellowish granular material. Lecithin stained with Sudan III, after impregnation in gelatin, also took a salmon-red color. It is obvious, therefore, that lecithin in substance, like the neutral fats, will take and retain the stain.

From these observations it may be concluded that the staining of solutions of the soluble soaps by Sudan III is due to their hydrolysis into fatty acids in which bodies Sudan III and Scharlach R are soluble and which are, therefore, colored by them.

After repeated solution and re-precipitation oleic acid and the neutral fluid fats stained by Sudan III retain their original

[4]Koch: *Zeit. f. physiol., Chem.*, 1903, xxxvii, 181.

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deep red color. Palmitic and stearic acids and cholesterin, on the other hand, become decolorized by this process and, therefore, can not be stained by these bodies. Lecithin gives a salmon-red color when stained with Sudan III. This is interesting because it places lecithin, so far as staining reaction is concerned, between the fluid fats and the soaps and solid fats.

According to Michealis,[5] the staining of fats by Sudan III is purely a physical and not a chemical process, but he admits that the physical properties of the body depend on its chemical character. He considered the union between Sudan III and oleic acid a physical one depending on the property of the unsaturated fatty compound in becoming oxidized. While this may be an explanation for the retention of the stain by the oleic acid, neutral fats and perhaps lecithins containing oleic acid radicals and the non-retention by the palmitic and stearic acids, the fact that other crystalline lipoids like cholesterin act similarly to the crystalline fatty acids suggest that the question as to the staining of the substance depends on its physical condition entirely.

This is particularly emphasized in the experiments with palmitic and stearic acid and cholesterin, where it was shown that when these substances were transformed by heat to their fluid condition they dissolved the stain immediately. On return to their solid state, however, they refused to retain the dye. Again those fatty compounds which at room temperature are fluids or semi-fluids are those which hold the stain even after repeated solution and reprecipitation.

This explains the cause of the discrepancies in the statements of various authors[6] as to the staining of fatty acids with Sudan III or Scharlach R.

It is believed that the results obtained warrant the statement that only those compounds of a fatty nature take these stains when they possess the physical characteristics of a fluid or semi-fluid at room temperature; other substances which allow of liquefaction by increase of temperature also react to the dye when in their fluid state. Such substances are butyric acid, oleic

[5] Ueber Fett Farbstoffe, *Archiv. f. Path. und Physiol.*, 1901, clxiv, 263.

[6] Daddi (L.): Nouvelle méthode pour colorer la graisse dans les tissue *Arch. Ital. de Biol.*, 1896, xxvi, 142: Rieder (H.): Ueber die Verwendbarkeit des Farbstoffes Sudan III in der klinischen Mikroskopie, *Deutsch. Arch. f. klin. Med.*, 1897, lix, 444; Handwerck (C.): Beiträge zur Kenntniss vom Verhalten der Fettkörper zu Osmiumsäure und zu Sudan, *Zeitschr. d. Wissensch. Mikroskopie*, 1898, xv, 177.

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acid, triolein, tributyrin and lecithin. Palmatic and stearic acids and their neutral glycerids and cholesterin come into this group when the temperature is above their melting point.

The results show that neither calcium nor sodium soaps, palmitic nor stearic acids will at room temperature take the stain with Sudan III or Scharlach R, hence the material staining by these substances which Klotz described as occurring at certain stages in calcareous degeneration can not be any of these compounds. In all probability it is a mixture of oleic acid, triolein and lecithin. This agrees with the findings which I have reported as a result of the chemical analysis of aortas in various stages of calcification.

GENERAL CONCLUSIONS.

1. The so-called proteid-soap compound of Klotz is not a true chemical combination, but a mixture made up mainly of fatty acids with small amounts of calcium soaps and globulin.

2. Sudan III and Scharlach R stain substances of fatty nature only when they are in fluid or semi-fluid. As oleic and butyric acid, triolein, tributyrin and lecithin are in this state at room temperature, they form a group to which must be limited the application of micro-chemical methods.

A CONTRIBUTION TO THE PATHOGENY OF SPASTIC RIGIDITY OF CHILDHOOD.

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PLATES I AND II.

It is not our purpose to enter into the discussion of the pathogenesis of all forms of rigidity occurring in infancy and childhood; the task would far exceed our resources and the question is too complex to be considered with any degree of fairness in this brief communication. The main object we have in mind is, to call further attention to the inadequacy of our actual knowledge of infantile rigidity and

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to the inexactness of our classification of the various spasmodic affections met with in infancy and early childhood. It is more particularly the anatomic facts underlying the close analogy which tetany bears, clinically, to the various forms of birth palsies that we desire to investigate. That this analogy is very great, there can be no doubt, if one is to judge by the frequency with which cases of so-called tetany have proved to be nothing less than some form of cerebral palsy of childhood and under which head we include, for the sake of convenience, Little's disease, spastic diplegia, chronic internal hydrocephalus, serous meningitis, etc., *i. e.;* all forms of cerebral lesion encountered in infants and young children and which have as main clinical manifestation—spastic rigidity of the extremities.

In other words, what is the anatomic substratum of the clinical symptom: spastic rigidity? is this the main or only external expression of any diseased state, or merely symptomatic of an otherwise clearly-appreciable pathologic entity?

But, in the first place, what is understood by tetany? "An affection characterized by peculiar bilateral tonic spasms of the extremities, either paroxysmal or continued" (Osler). The well known fact that the disease occurs under very different conditions and with all degrees in the completeness and severity of its symptomatic picture, would easily induce one to regard tetany more as a symptom-complex than as a distinct clinical entity; which view moreover would be more in harmony with what we actually know of its pathological anatomy, as we shall see later. It may well be however that tetany does possess a perfect autonomy; a supposition which would be all the more acceptable if the term tetany were applied only to the complete forms described by Escherich.

But then true tetany is an extremely rare disease, at least in this country. It is more common to see incomplete types of the affection, cases in which a few of the symptoms only are present, and not infrequently, some in which one of the so-called characteristic manifestations of tetany constitutes the entire clinical picture. The actual tendency however is not to regard such conditions (isolated carpo-pedal spasm for example) as instances of true tetany, but rather as symptoms of some other disease. It was, of course, only to the ill-constituted or atypical forms that we referred, when speak-

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ing of the difficulties which the differential diagnosis between cerebral palsy and tetany may present.

Aside from the multiplicity of its etiologic factors and the rarity with which it assumes the classic type, tetany still presents another peculiarity which would tend to minimize its chances of obtaining recognition as a distinct entity, and that is its occurrence, either fully or partially constituted, in conjunction with or as a complication of a number of other nervous diseases: Basedow's disease, cerebral and cerebellar tumor, syringomyelia, hysteria, epilepsy, etc.

Finally, other rare types of spasmodic affections in children have been recently described, which are closely analogous to tetany, such as the *Myotone spastique persistante de Hoschsinger,* or *Pseudo-tetanus of Escherich,* the underlying anatomic lesion of which is the *méningite cérébrospinale sèche.*

Neither of the cases about to be reported was definitely regarded as being tetany, but such was the diagnosis originally proposed in both; later, one case (cerebral sclerosis) was regarded as an instance of cerebral diplegia and the other (chronic internal hydrocephalus) considered to be cerebral tumor. In their clinical manifestations the two cases resembled each other very closely. Before giving a detailed description of the interesting histologic changes observed in the central nervous organs of these cases, it would be well to briefly consider, in the first place, the actual status of our knowledge concerning the pathologic anatomy of tetany.

The many observers who have seriously studied this question have not all reached the same conclusions, but they may be conveniently divided into two main groups:

(*a*) To the first group belong those (Schultze, Berger, Weigert, Loos, etc.) who, despite most scrupulous technique and careful microscopic study, have failed to find any appreciable changes in the central nervous system, and for whom, therefore, the pathologic anatomy of tetany remains entirely negative.

(*b*) Forming the second group, are a number of authors whose results have been positive, but to what limited extent these results are concordant, will presently be seen.

As regards first, macroscopic changes, it must be said that in those cases in which gross anatomic lesions did exist, they

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were either associated with some affection which tetany simply complicated, or else, were so combined or distributed as to render it impossible to isolate those underlying the manifestations of tetany.

Schultze found a patch of sclerosis in the upper cervical region and Traina pseudo-syringomyelic cavities in the cervical cord.

Köster described blood coagula upon the cauda equina, the cervical nerve-roots and along the course of the sciatic nerve.

Several observers have found, in cases of tetany, a slight serous infiltration of the membranes of the brain and spinal cord and even of the parenchyma of these organs, or, in other instances, a slight hyperemia of the same; all of which changes, however, practically remain within the limits of physiological reaction.

When it comes to the question of the histological changes observed in tetany, however, we are much better informed, as we possess more abundant data from which more definite notions can be derived. There have been numerous contributions to this particular chapter of pathology within the last decade, but we can only briefly analyse a few of the more important ones.

Langhans noted periarteritis and periphlebitis about the white commissure and anterior horns of the cervical enlargement of the spinal cord.

Pick, in the case of a young epileptic who developed typical tetany, found calcification of the smaller blood-vessels and fine arterioles especially of the centrum ovale and cerebellum. He is of the opinion that the narrowing and partial obliteration of the lumen of numerous blood vessels leads to the development of symptomatic tetany. A similar postmortem finding was observed in a woman who developed tetany secondarily to an operation for cataract.

Weiss examined the spinal cord of a child who had presented marked symptoms of tetany during three months following removal of the thyroid body. He found decided changes in the gray matter of the cervical cord. The ganglion-cells in great numbers were swollen and their nuclei displaced towards the periphery and often distinctly flattened. Vacuoles in both cell and cell-process were commonly observed. A number of cells were atrophied and their axones retracted

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within the cell-body. Aside from these changes which were especially prominent in the lateral group of the seventh and eight cervical segments, Weiss also found distinct spindle-shaped expansions of the axis-cylinder processes situated both in the anterior nerve-roots and in the central gray matter.

Changes similar to those described by Weiss have been observed by Bonome and Cervesato, Kirchgaesser and Katz in ordinary cases of tetany in children.

Bonome and Cervesato found in two cases of moderate intestinal disturbance, in which typical tetany developed only during the few days preceding death, very distinct changes in the gray matter of the cord. There was an appreciable atrophy of many ganglion-cells especially those of the mesial group; likewise atrophy with occasional varicose swelling of the nerve-fibres situated in the gray matter. In addition to these changes, there was noted a distinct proliferation of the neuroglia, which newly-formed tissue was often the seat of œdema and softening and consequent disintegration and cavity-formation; more especially were these irregular spaces observed in the gray matter. The authors regard the whole process as one closely analogous to poliomyelitis. The absence of paralysis in these cases, they attribute to the integrity of the lateral cell-groups of the anterior horns.

Katz noted in the case of a child, who, at the time of death, presented typical manifestations of tetany: cloudy swelling of the ganglion-cells of the anterior horns. The cells were granular in appearance and their nuclei indistinct. Furthermore, there existed the most extreme engorgement of the blood vessels about the cervical enlargement.

Kirchgaesser studied, with the aid of Marchi's method, the changes in the spinal cord in two cases of tetany in children and observed well-marked changes in the intramedullary segment of the anterior and posterior spinal nerve-roots, more particularly of the cervical and lumbar enlargements. In the anterior nerve-roots, the changes involved the entire axone from its origin in the multipolar nerve-cell. Similar alterations existed in the radicular filaments of the accessorius and hypoglossus, and even in the fasciculi solitarii and in the anterior commissure of the cord. The smaller blood vessels and capillaries were uncommonly distended but without appreciable changes in their walls. Absolutely similar changes

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were observed by Kirchgaesser in a case of (*a*) laryngospasm with facial phenomenon and in a case of (*b*) persistent spasm of the entire musculature without the characteristic attitude of the hands or other of the latent symptoms of the disease.

Ferranini and Rossolimo report the findings in cases of tetany associated with gastric dilatation. In one of the cases, a patient of twenty-three years of age, gastric disturbances had existed for over twelve years. The manifestations of tetany appeared thirty-three hours antemortem, and rapidly involved, with growing severity, the whole musculature of the body. At the autopsy, a distinct venous hyperemia of the pia as well as of the actual nervous parenchyma was macroscopically appreciable in both brain and spinal cord. Microscopically, well-marked changes were found more particularly in the medulla and in the cervical cord. Numerous nerve-cells were altered in various ways; frequently they were swollen and their pericellular spaces extensively dilated. These changes were especially prominent in the domain of the vesicular column of Clarke. Thickening of the cell-membrane and various stages of chromatolysis were commonly observed. Vacuolation of the cell-body was likewise fairly common. The nucleus itself was almost invariably deformed, decidedly enlarged, flattened against the periphery of the cell-body and now and then almost extruded from it. The cell-processes were proportionately thinned and often sharply bent upon themselves, or else presented varicose enlargements. No appreciable alterations were to be seen in the nerve-fibres.

Rossolimo refers to the changes observed in a subject, forty-three years of age, who had suffered from gastric disorders during the last fifteen years of life and in whom the most typical syndrome of tetany developed a few days antemortem. Aside from slight changes in the muscles, histologic examination revealed the presence of spindle-shaped swellings in the course of the axis-cylinder processes both in the anterior nerve-roots and in the peripheral nerves. There was also to be seen a varying degree of chromatolysis about the ganglion cells of the spinal cord in the vicinity of which the blood vessels were more often found markedly congested. The majority of nerve-cells however were relatively intact.

Peters in his recent monograph on the pathogenesis of the

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classic manifestations of tetany, gives a very exhaustive description of the lesions observed in three cases, and comes to the following conclusions:

1. Tetany is not a functional but an organic disease.

2. Its anatomic substratum is essentially constituted by an inflammation of the extra-dural connective tissue, which, extending into the intervertebral foramina, involves the dorsal nerve-roots together with their attached ganglia, leading thus to the development of (*a*) a neuritis interstitialis, (*b*) a gangliitis.

3. The primary pachymeningitis externa is characterized by the presence of: round-cell infiltrations, disseminated patches of epidural fibrinous or gelatinous exudate, hemorrhages along blood vessels whose walls are diseased. The hemorrhages are found more particularly in the intervertebral patches. The pachymeningitic alterations, although present in different places, are most marked and constant about the nerve-roots of the seventh and eighth cervical, the lower lumbar and upper sacral segments.

4. The neuritis interstitialis involves the motor as well as the sensory nerve-roots but is absolutely limited to their extra-dural segment. The peripheral nerves are free. Both the intra-dural and intra-medullary portions of the nerve-root are likewise usually intact; only occasionally do they present evidence of secondary degeneration.

5. The gangliitis manifests itself by (*a*) proliferation of the intracapsular endothelium with marginal vacuolization, (*b*) round-cell and leucocytic infiltration of the stroma between the nerve-cells which are thereby compressed, (*c*) degenerative changes of the cell-protoplasm (disintegration, karyolysis, etc.).

The author remarks that endothelial proliferation and protoplasmic cellular alterations are not peculiar to tetany, occurring in other affections which are characterized by the presence of contractures. But, the mode of development of these processes, especially the interstitial infiltration, does constitute a feature peculiar to tetany. The pachymeningitis externa is likewise characteristic of this disease. It was observed in all the cases, and furthermore, it involved only those nerve-roots whose area of peripheral distribution corresponded to the seat of clinical manifestations (spasms, con-

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tractures, etc.) and respected those corresponding to the peripheral regions which had remained free during life.

6. The more intense the pachymeningitis, the more severe the muscular contractures and the shorter the intervals between them; so that in very pronounced cases, the lesions may determine permanent tetanic manifestations in the affected limbs.

In three of the author's cases, certain peculiarities have seemed of particular interest to us for purposes of later comparison and we therefore make note of them in this connection.

In Case IV the author found: slight sclerosis of the brain, marked dilatation of the ventricles especially the fourth. Histologically: cellular agglomerations consisting for the most part of multinuclear leucocytes, were to be seen between normal cells and fibres and infiltrating both the gray and the white matter in the cord as well as in the brain. The author designates this process by the term Encephalitis interstitialis (luetica?).

In Case V chronic hydrocephalus of marked degree. A cross-section through the lower medulla showed distended capillaries and hemorrhages between the ganglion-cells of the subventricular nuclear collections. Accumulations of leucocytes in the perivascular spaces. These lesions were very marked and suggestive of encephalitis interstitialis.

In Case VII, marked congestion and slight œdema of brain, small punctiform extravasations in the course of the arteria spinalis anterior. In the posterior horns and in the intramedullary course of the posterior nerve-roots, degenerated areas were to be seen. Small round-cell and leucocytic infiltrations were found between the individual fibres of the motor nerve-roots.

Thus far, then, the histologic changes observed in the central nervous system by different authors may be summarized as follows:

Lesions which, in the first place, are essentially confined to the spinal cord and which involve more particularly the cervical and lumbar enlargements.

Lesions which vary in intensity all the way from simple engorgement of the blood vessels of the pia and central gray matter of the spinal cord (occasionally extending to the ad-

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joining portion of the medulla oblongata), to well-marked alterations of the ganglionic nerve-cells in the gray matter and more particularly of those of the motor groups; and changes in the nerve-fibres, likewise most pronounced in those fibres coursing through the central gray matter and in the intra and extramedullary segments of the spinal nerve-roots.

The ganglionic nerve-cells exhibited a most variable degree of chromatolysis, which, in certain instances, had gone so far as to lead to total disappearance of the cell. The nerve-fibres showed swelling of their axis-cylinders and loss, in greater or lesser amounts, of their myelin substance.

In addition to the changes included in the above synopsis and which practically embodies the joint-results of the great majority of observers who have written on this subject, there still remains to mention the lesions described by Peters (*i. e.* pachymeningitis, neuritis and gangliitis) who, as we have just seen, holds entirely different views from the rest as regards the pathogeny of tetanic manifestations; since he places the causative lesions outside of the dura and maintains that the central nervous organs themselves and the leptomeninges are entirely free.

All these facts, acquired in recent years and under all the favorable circumstances which our modern methods of technique and investigation ensure, deserve, certainly, to be carefully recorded, but nevertheless, they must be weighed even more carefully, accepted with caution and even with certain restrictions. In the first place, it must be stated, that, as far as alterations in the nerve-roots are concerned, Zappert observed destruction of nerve-fibres within the spinal nerve-roots in most children dying during the first year, although there had been clinically no symptoms whatever of nervous disorder.

It will be remembered also, that in a certain number of these cases, the manifestations of tetany were either associated with other conditions (epilepsy in one case reported by Pick), followed extirpation of the thyroid (probably of the para-thyroid as well) body, or else, developed antemortem, or very late, at least, in the course of some chronic affection of many years' standing and one which had seriously compromised the general nutritional integrity of the individual.

It would seem logical, in this connection, to admit that the

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lesions observed in the central nervous organs in the last category of cases (*i. e.* in cases of tetany following thyroid extirpation or prolonged disorders of nutrition), might be compared to those found in the spinal cord in a good number of cases of hæmic diseases, as in pernicious anemia, for instance. In other words, they might be regarded as the expression of nutritional disturbances, resulting, either from the loss or absence of some important and yet unknown element concerned in the neutralization of certain toxic principles elaborated in the course of metabolism (as in the case of parathyroidectomy), or from an insufficient elaboration or production of active cells, an adequate supply of which is the indispensable prerequisite to the maintenance of nutritional equilibrium (a deficiency realized in case of disease of the hæmapoietic organs).

In tetany, it is true, the lesions are to be found more particularly in the central gray matter, it is the ganglionic nerve-cell of the anterior horn which suffers most or bears the brunt of the invasion; whereas in pernicious anemia and kindred affections, it is a sclerosis of the white columns which is most commonly observed. But there is here, merely the question of selective action of underlying toxic principles and we are of the opinion, that the prime factor in producing both categories of changes, is unquestionably constituted by some toxic agent freely circulating in the system.

It must be said, moreover, that, cellular changes absolutely analogous to those described in connection with tetany, have been observed in different pathologic conditions which affect, similarly to pernicious anemia, the general nutrition, and without having given rise to any of the clinical manifestations characteristic of tetany; in such conditions for instance as Addison's disease, operative myxoedema, lesions of the pancreas, as well as in the various forms of auto-intoxication: uræmia, acute yellow atrophy, intestinal auto-intoxication, etc. Uræmia is mentioned by Osler, as one of the conditions with which tetany may be associated, and it is a question, in our mind, if those cases of tetany which develop in the course of gestation are not of the same origin.

Then again, aside from these vitiated nutritional states, in which the cellular changes are attributed to the noxious influence of some toxic principle elaborated within the system, there is still

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a series of poisons belonging to different classes, which are capable of inducing similar changes within the central gray matter of the spinal cord.

(1) Toxins derived from suppurative or necrotic processes. Blood and cardiac poisons.

This class produces the cellular changes known as tigrolysis, and also swelling of the cell-body and varicosities in the course of the cell-processes.

(2) Among mineral poisons, the most prone to determine cellular alterations are: arsenic, phosphorus, potassium chlorate, antimony, chlorhydric acid. It is to be noted that phosphorus is mentioned by Oppenheim, as the mineral poison the most frequently concerned in the production of tetany.

(3) Of the organic poisons, alcohol is by far the most important. The cellular changes occurring in chronic alcoholism and delirum tremens have been abundantly described. The alkaloids, more particularly strychnine, morphine and cocaine are susceptible of inducing analogous changes.

It may be mentioned that alcohol and morphia are recognized etiologic factors in the determination of tetany (Osler).

(4) Toxins associated with the various infectious processes: Diphtheria, tetanus, cholera, etc.

In children the influence of the acute infectious diseases in determining tetany is well-recognized, and cholera is mentioned by numerous authors as one of the infections most commonly associated with tetany.

As will be readily seen, the foregoing tabulation of the various agents of a toxic nature (whether bacterial, mineral, organic or derived from the products of defective metabolism) capable of inducing cellular alterations in the spinal cord, practically includes all the factors actually recognized as possible causes of tetany. Reasoning from this fact, it would seem logical to maintain that the cell-changes described in connection with tetany by different authors, and which we have in the main incorporated in the beginning of this article, cannot be regarded as constituting, properly speaking, the anatomic substratum of tetany. It would be more accurate, perhaps, to consider them simply as the expression of the reaction determined in the nervous parenchyma by a sufficient grade of toxemia, whatever its origin or character.

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The importance of this latter consideration will become more apparent, when, after describing the findings in our actual observations, we come to the discussion of the pathogeny of the symptoms to which they gave rise.

Neither of the cases which form the ground-work of this contribution have we had the occasion of studying clinically; we can, therefore, only transcribe the main points in the clinical histories as they appear in the hospital records. But being reliably informed concerning the difficulties which diagnosis offered in both these cases, and the examination of the central nervous organs having moreover been entrusted to us, the findings appeared sufficiently interesting to merit publication.

CASE I. B. S., age one year. Female.

CLINICAL HISTORY.

Family History.—Mother apparently epileptic, gives history of fainting spells with loss of consciousness. During a period of three days and coming on, on the sixth day after the birth of her child, the mother had convulsions during which she bit her tongue. Since birth, which was protracted but not instrumental, the child presented the following condition: Hands contracted and head drawn back. The child had always acted queerly not noticing anything about her and apparently not knowing her mother. Began to have convulsions at three months, numbering from ten to twelve in twenty-four hours; they became much more severe during the last weeks of life. At the same time, it was noticed that one foot was turned in. The convulsions were characterized as follows: The limbs of the left side were drawn up, i. e., flexed and twitched slightly, whereas the right arm and leg would become extended and stiff.

At other times, i. e., in the intervals between these convulsive attacks, the child would lie with the arms flexed at elbow and with both fists clenched, the thumb being slightly held in palm of hand by the other fingers flexed strongly upon it. The legs would be fully extended with slight adduction of left leg and foot, and the toes changing position almost constantly, but those of left foot generally held in a state of plantar flexion. Head drawn slightly backward and face turned sharply to the left; neck moderately stiffened; eyes rolling about from side to side and often upwards as well; pupils equal and contracted; child apparently blind. Anterior fontanelle open, posterior not completely closed. Slight motion still present at lambdoid suture. Palate rather high. On the under surface of anterior part of tongue and extending also over floor of mouth is a shallow ulcer about one centimeter in diameter. On lower lip of child considerable fine pigmented hair—on chin fine downy colorless hair.

Abdomen distended, soft, edge of liver felt about one centimeter below costal margin.

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Later Notes.—Arm and legs held stiffly, passive motion most difficult especially at elbows and knees; resistance slightly greater on right side. Left arm and leg on measurement are slightly smaller than right. Impossible to straighten fingers and toes.

Spasm of muscle less than on entrance. Child apparently blind. No Babinski reflex on either side. Head symmetrical.

Notes at time of autopsy, October 17, 1905, taken from official records of the Bender Laboratory, read as follows:

Autopsy Record, 0-942. Autopsy by Dr. Pearce, October 17, 1905, at Child's Hospital. Brain only removed.

Clinical Diagnosis.—Tumor of brain; Broncho-pneumonia.

Head.—Of average size. On stripping scalp the anterior fontanelle is slightly open, irregular in shape and tense but not bulging. Posterior fontanelle is closed. The bones of the skull are in apposition except at anterior fontanelle but are not united; by pressure they can be readily moved one upon the other. On removing calvarium the dura is seen to be tense and fluctuant; on section a large amount of clear fluid escapes.

Brain.—Convolutions are flattened. Blood vessels are prominent and deeply congested. Both hemispheres are fluctuant and on attempting to remove the brain from the cranial cavity a rupture along the inner aspect of the left hemisphere occurred with escape of a large amount of clear fluid. Each hemisphere is found to be transformed into a sac lined by smooth greyish-white membrane in which blood vessels are very prominent. The cortex is greatly thinned varying in thickness from two to six millimeters except at the most anterior portion of the frontal lobes where it was about a centimeter in thickness. The dilation of the ventricles is extreme. The third ventricle is greatly dilated as is also the *iter a tertio ad quartum ventriculum*. The fourth ventricle is slightly dilated; this dilatation extending somewhat laterally. The corpora quadragemina and basal ganglia are very prominent. The prominence is due in part to the atrophy of the adjacent structures. Cerebellum shows no changes. The choroid plexuses are slightly congested. Owing to disturbance of relations brought about in removing the brain it is impossible to examine the communications between the ventricles other than those noted above.

Anatomical Diagnosis.—Congenital internal hydrocephalus.

The above description of the macroscopic appearance of the brain might be rendered more complete by inserting a few additional remarks. There are patches of leptomeningitis (thickening and opacity of the membranes) over the occipital pole on all its surfaces and in the fossa Sylvii in the right hemisphere, and over the mesial surface as well as along the inferior border of the occipital lobe in the left hemisphere.

There is evidence of microgyria in various places, but it is most distinct about the motor convolutions of the right hemisphere, the inferior frontal and the inferior parietal convolutions of the left hemisphere. Patches of ventricular meningitis, most marked over the

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ventricular surface of the caudate nucleus are distinctly to be seen in both hemispheres, but the lesions are far more extensive in the left lateral ventricle, where a relatively thick, creamy-white, pulpy exudate covers the seemingly enlarged head of the caudate nucleus, spreading out irregularly from that point over the outer wall of the ventricle and into its anterior cornu, and invading more or less diffusely the proximal surface of the parietal segment of the lateral ventricle. The exudate is thickest over the most mesial portion of the caudate nucleus along the stria cornea, and in the vicinity of the foramen of Monro where it partly covers over the larger ventricular blood vessels.

The brain-stem presented a very peculiar aspect; there being, in the first place, a decided asymmetry between the two lateral halves of its various segments (peduncle, pons and medulla). This portion of the brain having been separated from the hemispheres at the level of the anterior corpora quadrigemina and nuclei rubri, *i. e.*, well up in the course of the crura cerebri (despite the unfavorable condition of affairs resulting from the unavoidable tear at the time of removal of the brain as well as from subsequent handling and faulty positions in jars, the hemispheres having fallen completely asunder), and the part being held vertically, there is noticed a decided deflection or inclination of the brain-stem to one side, seemingly due to atrophy of this side; this atrophy affecting about equally the various segments from the subthalamic region to the motor decussation. Not only is one lateral half shorter, but also decidedly lesser, in size; the disparity in the volume of both halves of the brain-stem being most manifest.

The anterior median fissure of the cord continues upward uninterruptedly over the pons and then becomes lost in the interpeduncular space. Of the anterior pyramids, there is barely a trace; the inferior olives being very prominent although of very unequal size, and bulging on either side of the median fissure, where they truly form the ventral boundary and substance of the medulla. It is in the region of the pons that the greatest asymmetry appears. One has the impression that the superficial transverse pontine fibres are wanting on one side; which would explain the existence of a deep fissure over the ventral surface of this region and contribute much to render one lateral half of the pons both shorter and smaller.

The Fourth Ventricle.—The floor of the fourth ventricle presents nothing particularly atypical, save that its lateral angles are pressed outward and forward, whereby the ventricular floor at its widest part is much more plane than in the normal state. The cavity of the fourth ventricle as a whole, moreover, is considerably dilated, much more so than is usually seen even in cases of marked hydrocephalus.

Rigorously serial sections of the entire brain-stem; portions of the cortex of the ascending central convolutions, the para-central lobule, the calcarine region and the cerebellum; as well as portions of the ventricular surface of the caudate nucleus at the level of the ependymal lesions, together with the optic nerves, have been sub-

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mitted to microscopic study. The cord, as already said, had not been removed. Staining methods employed: Weigert and Pal for myelin-sheaths; Pal-cochineal; Van Gieson, hematoxylin-eosin, and carmin.

Description of Histologic Findings.—At the level of the peduncle and upper segment of the pons Varolii (Pl. I, Fig. 1), microscopic examination reveals the well-marked atrophy of one lateral half of this portion of the brain-stem. Both fasciculi longitudinales posteriores, both bundles of radicular trochlearis filaments, both brachia conjunctiva and both masses of fibres forming the crura cerebri (Füsse pedunculi) are present, but aside from the pyramidal bundles, whose relative proportions, differences of topographic distribution resulting from the absence of certain systems of fibres render unascertainable, all the above-named tracts are decidedly atrophic on one side; the disproportion being most manifest. There is but one mesial fillet and that on the atrophic side, where, on the other hand, only a trace of the lateral fillet exists; whereas on the healthier side, one sees what appears to be a perfectly typical nucleus of the lateral fillet, there being no indication whatever of a mesial fillet. There exists but one corpus quadrigeminum posterius, which is situated on the atrophic side, and but one set of superficial and deep transverse pontine fibres; their corresponding territory on the opposite side cannot even be said to be occupied by reactionless, non-staining degenerated fibres. The result of this anomaly is, that as we consider successively lower cross-sections of the pons, one pyramid, or rather one mass of fibres including the motor pyramidal fibres and the cortico-cerebellar tract, appears free at the ventral border, whereas its fellow follows the usual course between the two sets or layers of transverse pontine fibres; being covered ventro-laterally by coarse bundles, either transversely or vertically directed, and which evidently belong to the brachium pontis. These fibres cease abruptly at the anterior extremity of the median raphe. At lower levels, a fair number of these fibres pass dorsally to the free mass or corticipetal fibres of the opposing side, thus constituting, at least apparently, what might be called a deep set of transverse pontine fibres for the atrophic hemi-pons.

Small lesions are present along the ventral periphery (occlusion of vessels, infiltration, corpora granulosa), sink in behind the pyramids; they also exist over the ventricular floor and angles and even in the central griseum, extending along the raphe from the ventricular floor into the deeper structures of the tegmentum.

The floor and lateral recesses of the fourth ventricle present a good number of infoldings, and the medullary vela are markedly thinned, showing to what extent ventricular dilatation has occurred as well as the results of chronic inflammation (determination of adherent surfaces in pockets of main sac). An interesting anatomic detail at this level, is the unusual sharpness of outline of the fasciculus predorsalis of Tschermak.

In the lower regions of the pons, the fibres of the brachium

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pontis, which (at high levels), were confined to one lateral half of the organ, embracing on all sides one set of corticifugal fibres and which, lower down, penetrated, as already said, into the atrophic side, passing dorsally to the great mass of free pyramidal and cortico-cerebellar fibres, now gradually collect at the ventro-lateral periphery of this side (i. e. the atrophic side), lying just outside of the pyramidal tract, which, we repeat, they cross or cover over ventrally, at no point whatever, leaving thus this pyramidal tract perfectly free at the anterior border of the pons Varolii throughout its whole extent.

Just how the brachia conjunctiva leave the tegmentum to pass into the cerebellum (their course being, of course, just the reverse) is not clear, the fact being that the roof of the ventricle is nowhere intact. Higher up, a thin blade of white matter containing well-stained fibres, in which the outgoing filaments of the patheticus can be distinguished, as well as other fibres evidently belonging to the superior cerebellar peduncles, leaves no doubt that we have to do with the valve of Vieussens, but it must be said that such a process exists only on one side, the other half having disappeared; a fact one readily conceives on seeing the extensive lesions which have occurred at all points along the floor and more especially at the lateral angles of the ventricle, corresponding to the acoustic nuclei, the restiform bodies, etc. The process has even gone so far as to disrupt the cerebellar substance intervening between the nucleus dentatus and the tuberculum acousticum. In part at least, the fibres of the brachia conjunctiva seem to join those of the brachium pontis at the side of the pons. Still lower, near the ponto-bulbar junction, the fibres of the brachium pontis abandon the field situated to the outer side of the pyramid, trend backward and seem to blend with the most superior extension of restiform body of that side (i. e. the atrophic side), then to curve outward and merge into a dense tangle of deep-staining fibres which is capped over by cerebellar folia.

The cross-section of the fasciculi teretes and of the posterior longitudinal bundles appears perfectly normal. Both the motor and sensory pontic nuclei of the trigeminal nerve are distinctly recognizable, as is also the descending or spinal root of this same nerve. A point which is of particular interest, being given the scantiness of our knowledge concerning this special detail in nervous anatomy, is the distinctness with which the relationship between the trigeminal system and the cerebellum can be studied. Continuity of decussating trigeminal fibres with outgoing radicular filaments—the passage of fibres from the vicinity of the fifth nuclei and from their decussating field into the cerebellar hemispheres, by way of the lateral ponto-cerebellar angles, their relations to the fasciculi teretes, etc., are all details which are most clearly appreciable. At this level also, both bundles of pyramidal fibres begin to resemble each other somewhat more distinctly than heretofore, and there is, apparently at least, a partial restoration of the wanting mesial lemniscus. Both abducens nuclei as well as their outgoing radicular filaments come

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prominently into view, as do also the subventricular loop and outgoing roots of both facial nerves; the first part of the latter nerve, that which, after its origin, courses dorso-mesially to encircle the abducens nucleus is less clearly appreciable. The same may be said of the nucleus of origin of the facial. Whereas, on the relatively healthy side, the abducens root-fibres emerge at the ventral border, those of the atrophic side leave the pons at the bottom of the anterior fissure which is quite deep at this level. Irradiation of the root-filaments of the trigeminal nerve into their pontic nucleus, is very distinctly to be seen on the healthier side of section. A plexiform network situated dorsal to the pyramidal tracts on either side seemingly represents the system of the corpus trapezoides. Its fibres decussate in the median raphe and literally traverse, in part, the restiform body, as if going to the cerebellum, but in reality, they come into relation with a collection of ganglionic nerve-cells located to the outer side of the restiform body and which probably belongs to the ventral acoustic nucleus; this nucleus having acquired abnormal relations to the surrounding structures owing to the very considerable displacement which has resulted from the extensive lesions involving the bulbo-ponto-cerebellar angle. This view receives additional support as we consider lower sections, i. e. sections passing slightly above the level where the inferior olives come into the field, when there appears just outside of the fully-developed restiform body, a long vermicular collection of ganglionic nerve-cells which borders on the dorso-lateral periphery, curves forward along the ventral aspect of the restiform body and receives the fibres of the cross-coursing bundle attributed above to the system of the corpus trapezoides. This cellular collection is doubtless part of the ventral acoustic nucleus with its tuberculum acousticum. At this level, it is impossible to outline the pyramidal tract on the atrophic side, but it is still fairly well-defined on the opposite side. Both crescentic areas occupied by the descending spinal roots of the trigeminus are clearly defined and practically normal in appearance. The restiform body of the healthier half of this region cleaves into two distinct deep-staining diverging areas, between which, a lighter field oblong in shape and poor in medullated nerve-fibres gradually develops. The posterior longitudinal bundles gradually unfurl beneath the mesial portion of the ventricular floor and slowly trend forward along either side of the raphe. The trapezoid formation is gradually replaced by the cerebello-olivary system.

Lesions of the ponto-peduncular level.—Lesions abound along the ventral periphery, penetrating into the interpeduncular recess, where a large almost empty lenticular cavity exists; giving the impression that it has resulted from softening associated with arterial occlusion. Other lesions are found at the lateral periphery behind the mass of fibres of the "füsse pedunculi," dipping down into the substance proper of the organ, completely severing the most superior part of the brachium pontis, and furthermore interrupting, but only on one side, the mesial fillet at its angle of union with the lateral fillet;

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it has thus determined practically its total degeneration. These foci are in relation with vascular alterations of considerable intensity, which are to be found all along the ventral periphery, to a lesser extent along the lateral borders, but also at different points in the ventricular floor of the region. There is distinct evidence of a chronic leptomeningitis and ependymitis. The main vascular trunks appear relatively reduced in their general proportions on cross-section, but their walls are enormously thickened and fibrous in character. These blood vessels often appear as small round or oval structures, constituted by concentrically disposed, somewhat glistening, slightly wavy fibrous layers, occasionally occluded entirely, more often containing a few cells in their lumen, but rarely containing many; in which latter case the vessel-wall is only slightly thickened and its lumen occupied by a few shadow-cells. A number of vessels take a very black color in hematoxylin-stained sections or appear as blackish masses, which, with the high-power, are seen to be made up of equally black spheric cell-like bodies of unknown origin and character. The lumen of many blood vessels is filled with an admixture of these dark-staining black bodies and shadow-cells, both of which are equally to be found in the adventitial spaces of some of them. In between the various vessels, and lodged in the interstices of the leptomeninges, there is present a great variety of elements: granular detritus, apparently a few leucocytes, shadow-cells, a fair amount of blood-pigment with occasional refractive crystals, a few endothelial cells, granular cells containing particles probably derived from disintegrated tissue, occasional amyloid corpuscles and fibrous wavy strands. Less intense but analogous changes, are also observed about the Sylvian aqueduct and ventricular floor. Occasional thrombosed vessels in the depth of the organ are also seen, noticeably in the vicinity of the oculomotor nuclei, much more marked on one side, where the cells of the nucleus appear distinctly atrophied in comparison with those of its fellow, which, despite very appreciable lesions of like character, shows the presence of remarkably well-preserved ganglion-cells. It must be said that vascular alterations are also present in the substance proper of the brain-stem, being practically confined however to the peripheral zone, where the blood vessels show distinct increase in number; many having decidedly thickened walls and their lumen being often either partially or completely occluded.

Interesting changes are to be noted about the Sylvian aqueduct and the floor of the fourth ventricle. The exact location of the aqueduct is readily recognized owing to the persistence, at one point, of the regularly disposed line of ependymal basal cells, with fully-preserved details of morphologic structure. These cells have proliferated and form a thick compact limiting barrier; from their deep surface, emerge the characteristic basal processes which penetrate into the substance of the subventricular griseum. The roof and sides of the Sylvian aqueduct have been completely undermined and present a jagged and irregular outline; the ependyma has been destroyed

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and replaced by numerous cells of peculiar morphologic type. They are numerous, rounded in outline, remarkably uniform in size, resembling in general texture the ependymal cell, but much smaller, and instead of being diffusely and finely granular, they possess a much clearer matrix with only two, three, or four diminutive deep staining, bluish-black, dot-like granules, lying far apart from one another with intervening clear matrix. We are totally ignorant of their source and character. The possibility suggests itself that they are newly-formed, immature (judging from already specified proliferation of the same) ependymal cells, or the same, altered by disease, as they do resemble glia cells, such as are seen in different pathological states. These cells are either imbedded in the neighboring parenchyma, or lying free in the cavity along with a greater or lesser amount of degenerative products: granular debris, red blood cells, pigment, granular cells, etc. Scattered through the deep gray substance surrounding the aqueduct, are a number of large cells with rather indistinct markings, but which resemble in a general way, the classic multipolar ganglionic-cell.

The floor and lateral recesses of the fourth ventricle present analogous lesions at various points, but, with the exception of two small foci situated in the middle line and corresponding to the origin of the raphe, these lesions are most extensive in the more lateral portions of the floor and about the ponto-cerebellar angle. Practically over the whole extent of the ventricular floor however, slight changes have occurred, and almost everywhere, the basal ependymal cells are decidedly altered, appearing as jet-black, round or oval bodies, the true nature of which it would be impossible to appreciate, if it were not for the slender processes which can be seen to emerge from under them, and stream ventrally towards the raphe through the subjacent nervous parenchyma. At several points the ependymal line is interrupted; it is most normal near the origin of the raphe. Occasionally, it becomes reduplicated, forming infoldings or tubular prolongations which dip down into the subjacent griseum a varying distance. Two of these infoldings situated at the lateral angles, are larger than the rest, and deserve to be briefly described. One involves the subventricular gray matter dorsal to the descending cerebral trigeminal root on the healthier side; the other is situated under cover of the posterior corpus quadrigeminum on the atrophic side, extending very deeply into the formatio-reticularis and actually bisecting the intra-pontine segment of the brachium conjunctivum at the angle of union of its two blades. At both these points, owing to the presence of a number of fairly normal ependymal cells, the mechanism of this process can be clearly made out. A true invagination of the ventricular floor has occurred, forming an extremely narrow tubular prolongation closely resembling a tubular gland, the walls of which, formed by closely-packed proliferated ependymal cells, are here and there absolutely in contact, thus producing an alternating series of atresiae and dilatations. These lining cells are very regularly disposed, take sometimes the normal stain, but often

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are replaced by jet-black globular bodies similar to those previously mentioned in connection with the lesions of the general ventricular floor; again, are intermediate forms observed, i. e., cells which are only partly laden with black granules, so that their texture is partly visible. It would seem that these black granules might represent the products of degeneration, and that the containing cells are truly ependymal cells, or else modified glia cells, which have taken on phagocytic activity. In many places, the ependymal cells have proliferated even to the point of forming local agglomerations, disposed in parallel rows three or four cells deep, and presenting in a very characteristic fashion a regular "shoal arrangement." In the lumen of the tubular infoldings thus determined, and about the ventricular surface at their point of dipping in, much free detritus exists, containing pink or violet (according to stain) staining cells, rounded or oval in outline, and the structure of which is identical with that of the ependymal cells (perhaps a different stage of development and representing a proliferating embryonal type), also the type of cell above described and which is characterized by the presence of isolated dot-like blackish granules in a clear matrix, as well as blood-cells, granular detritus, blood-pigment and occasional classic granular cells. Near the elevated ventricular edges of these tubular prolongations, it is common enough to see peculiar shred-like collections or tufts, evidently formed by the aggregation of a great number of ependymal processes or fibrils. The lesion located beneath the corpus quadrigeminum posterius invades its ventricular surface to such considerable extent, that fairly large cavities have been formed, resembling that described in connection with the lesions of the interpeduncular griseum, and like it, probably the result of vascular obliteration. All around these various lesions, marked changes are present in the blood vessels: thrombosis, thickening, extravasations composed of granular cells, blood pigment, etc. If distinct evidence of a true meningitis is scant at other points along the brain-stem, it certainly abounds over the dorso-lateral border of this segment of the pons, where lesions of considerable intensity are to be seen in the pia covering the posterior corpus quadrigeminum and the adjacent portion of the pons; extreme fibrous thickening of the vessel-walls, occlusion of the lumen with densely packed granular bodies and shadow-cells.

In the thickened meshes of the pia are lodged: desquamated endothelial cells, shadow-cells, granular bodies, granular detritus and blood-pigment. The whole process certainly resembles very closely the lesions observed in syphilitic meningitis (endarteritis obliterans, chronic fibrous thickening, involvement of the subjacent nervous parenchyma, absence of ordinary inflammatory reaction, i. e., of polymorphonuclear leucocytes, limited areas of softening, main localization in the leptomeninges, involvement of the optic sheaths, vascular alterations in the peripheral zone of the nervous parenchyma, etc.).

At the level of the full development of the auditory system (Pl. I, Fig. 2), a very peculiar anomaly presents. Owing probably in part

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Plate II

To Illustrate Drs. Archambault and Baldauf's Article on "A Contribution to the Pathogeny of Spastic Rigidity of Childhood."

Albany Medical Annals, January, 1908.

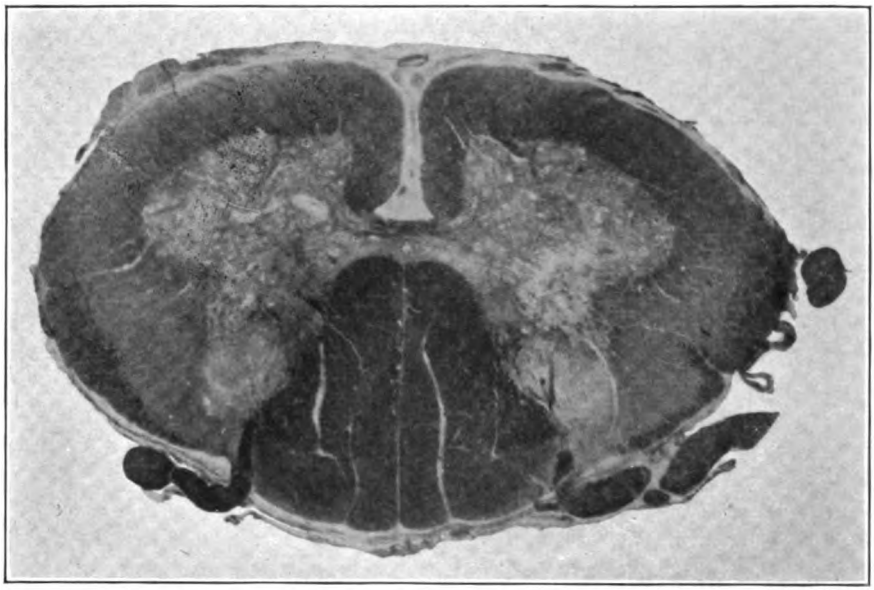

Fig. 4

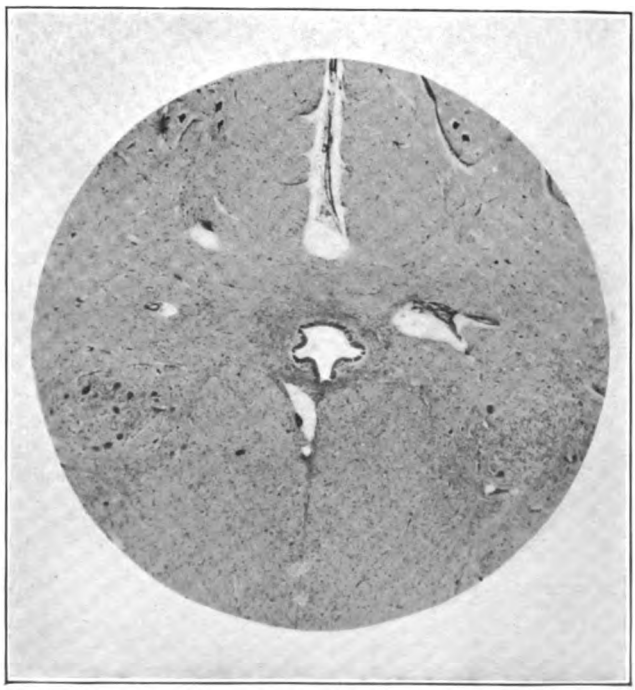

Fig. 5

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nants of former miliary hemorrhages are to be seen, or else, actual cavities mark the site of the destructive process. At the level of the seventh and eighth cervical segments, larger lesions of a similar character are situated at the base of one posterior horn, which is for the most part destroyed, as well as the surrounding substance of the intermediate gray matter; the base of the anterior horn being involved only to a very limited extent. The whole process resembles most closely that of poliomyelitis anterior acuta in its later and stationary stage. The multipolar nerve-cells of the anterior horns are in a general way quite well-preserved. Similar lesions are found throughout the dorsal and lumbo-sacral regions, where they surround on all sides the vesicular column of Clarke without actually involving it to any appreciable extent, except at a few levels, where it is decidedly implicated.

The cortex of the Rolandic and calcarine regions shows everywhere most distinct alterations. Meningeal changes are present, consisting in marked thickening and round-cell infiltration of the pia, thickened and obliterated blood vessels in the perivascular spaces of which, as well as in the meshes of the pia, large numbers of granular bodies are to be seen. The molecular zone of the cortex is rarefied, presents a clouded and porous aspect, and is strikingly poor in tangential fibres. The large pyramidal-cells are moderately reduced in number, but their finer structural details are markedly inappreciable. The neurogliar meshwork and glia-cells are distinctly increased in their proportion to the parenchymatous structures. Throughout the cortex, vascular lesions and miliary cavities are distinctly visible.

Resumé and Interpretation of the Secondary Degenerations, Atrophies and Failures of Development Observed in Each Case.

In Case I, there is a moderate and diffuse degeneration of both pyramids; a degeneration of both mesial fillets, total on one side, partial on the other; a total degeneration of one lateral fillet and of one set of antero-external arcuate fibres; an incomplete but marked degeneration of both sets of internal arcuate fibres. There is a marked atrophy of one olive and one corpus quadrigeminum posterius,and a generalized atrophy of one-half of the brain-stem. There is total absence of one set of superficial and deep transverse pontine fibres, and of lateral half of the valve of Vieussens.

The degeneration of the pyramids is due to the numerous foci of perivascular disintegration situated in the overlying meninges, about the raphe, and even within their own territory at various levels throughout the brain-stem. The degeneration of the internal arcuate fibres on both sides, of one mesial fillet and one set of antero-external arcuate fibres, is in direct relation to the pericanalicular destructive lesions of the lower medulla, which involve the central gray matter situated in the middle line and in the domain of the nuclei gracilis

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et cuneatus of one side. The total degeneration of one mesial fillet in the ponto-peduncular region is merely the result of its actual involvment at the level of the extensive lesions previously described; it being in part reconstituted, as we have seen, in lower regions. The total degeneration of one lateral fillet is in relation with the extensive lesions involving the contralateral acoustic nucleus and tuberculum acousticum, and which at the same time, explain, the consequent atrophy of the related corpus quadrigeminum. The marked atrophy of one olive is due to the segmentition and partial destruction of the heterolateral restiform body. It is well to state in this connection, that the process which this olivary body exhibits, is distinctly an atrophic and not a degenerative one, properly speaking; a fact which would tend to show that the so-called cerebello-olivary tract is derived, in good part at least, from the olive and not exclusively from the cerebellum. The hemi-atrophy of the entire brain-stem is evidently in direct relation to the extensive lesions, situated, throughout the pons and medulla, about the lateral angle of the fourth ventricle on the opposite side. The crossed relation between the various segments of the brain-stem and the cerebellum, as well as the important share which the connecting systems have in the constitution of the brain-stem, are facts so well-known, that the mechanism of this hemiatrophy hardly needs further discussion. The absence of one-half of the valve of Vieussens and of one brachium pontis, is the result of their actual implication in the various destructive processes observed both about the ventricular floor and along the ventro-lateral periphery of the ponto-peduncular region.

In Case II, we note an appreciable degeneration of both pyramidal tracts throughout their course, as well as of both mesial fillets; a fairly marked degeneration of both antero-lateral ascending tracts; a very extensive degeneration of the descending trigeminal fasciculi below the level of the sensory decussation; a discoloration of the prepyramidal area in both lateral columns of the spinal cord. There is likewise, a very marked atrophy and degeneration of one red nucleus, the source of which we have already sufficiently exposed. The degeneration of the motor tracts is evidently the result of the cerebral sclerosis which was well-marked in this case; but, in the spinal cord, the area degenerated in either lateral column far exceeds the proportions ascribed by classic authors to the territory of the crossed pyramidal tracts, and we are of the opinion that other degenerated tracts contribute to the topography of this uncommonly large field of sclerosis. The lesions observed beween the red nuclei and upon which we have particularly insisted, involve the exact seat of decussation of the rubro-spinal tracts, described by von Monakow. These tracts, one for each side, take their origin in the red nuclei, decussate in the median raphe, course through the pons and medulla where they occupy the antero-lateral segment of the formatio-reticularis, and in the cord are situated immediately in front of the crossed pyramidal tracts, finally terminating, in part at least, like the latter, about the multipolar nerve-cells of the anterior horns. So

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far and to the best of our knowledge, the existence of this tract has been positively demonstrated only in the lower animals; without making any assertion with regard to the fact, it seems to us that the actual observation is quite favorable to the hypothesis that the rubro-spinal tract exists likewise in man.

The degeneration of both mesial fillets (more marked on one side) and both descending trigeminal fasciculi in the spinal part of their course. is entirely referable to the bilateral and extensive changes situated in the domain of the nuclei of the posterior columns and which we have fully described in connection with the histologic appearance of that region. The unequal but bilateral degeneration of the antero-lateral marginal fields of the upper dorsal and cervical cord, is the result of the well-marked vascular changes observed about the intermediate gray matter and the proximal portion of the anterior and posterior horns. The sclerosis is probably not limited to the tract of Gowers, but all that our actual knowledge of the anatomy of this region permits to state, is that degeneration of this tract on both sides is unquestionable.

Resumé of the Lesions Common to Both Cases and Discussion of Their Analogy With the Lesions of Tetany.

Although internal hydrocephalus and cerebral sclerosis are entirely distinct pathologic entities, the respective constituent lesions of which have nothing in common, not only with each other, but also with the lesions described in connection with tetany, it must nevertheless be stated that in both cases actually under consideration, well-characterized changes exist, which do not form part of the process associated with the determination of either internal hydrocephalus or cerebral sclerosis; or, if they do (which, in our belief, is not improbable), mention of them is still wanting, to the best of our knowledge, in the classic description of these morbid entities. These additional lesions which are identical in both cases, are likewise identical, or almost so, with many of the changes described in tetany.

The accessory changes to which we have reference may be briefly summarized as follows:

(*a*) Vascular and interstitial changes, occurring more especially in the leptomeninges of the brain-stem and spinal cord (available in one case only) and about the structures forming, or neighboring upon, the limiting walls of the Sylvian aqueduct, the fourth ventricle and the central canal of the spinal cord; occasional foci also existing in the substance proper of these organs. These changes consist in marked thickening of the

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walls more especially of the medium-sized and smaller blood vessels; partial fibrous obliteration of a few, cellular occlusion or thrombosis of many, of them; perivascular dilatation and distinct evidence of chronic fibrous leptomeningitis and ependymitis; marked thickening of the sub-pial and peri-ependymal neurogliar layers.

(*b*) Parenchymatous changes, situated for the most part in the vicinity of, and certainly partly dependent upon, the lesions included in the first group, disseminated throughout the central griseum of the brain-stem and spinal cord. These alterations are represented by various types of cellular degeneration and vary considerably in intensity from one level to the other; including all degrees of simple atrophy and cloudy swelling, loss of pigment or of the nuclear and nucleolar elements, distortion of contour and even total disappearance of the ganglion-cells. We are excluding, of course, the nuclear changes resulting from actual implication of the gray matter in the destructive ventricular lesions which were observed in both pons and medulla (as for instance, the extensive involvment of the acoustic nuclei, the nucleus cuneatus).

It is interesting to note in this connection, that in both cases, the nuclear lesions are practically confined (with the exception of the acoustic nucleus and tubercle, extensively involved in one case) to the same structures, namely: the nuclei of the posterior columns, the nuclei of origin of the oculomotor nerves, the nuclear field ventral to and between the nuclei rubri.

In drawing points for comparison between these various lesions and the changes described by most observers in connection with tetany, we notice, in the first place, that either category of changes just described has been advanced as representing the underlying anatomic cause of the tetanoid manifestations; the parenchymatous by the majority, the vascular and meningeal by a few, of the authors.

As regards first the latter class of lesions, which were well-marked in both our cases, it will be remembered that absolutely similar findings were described by Langhans, and especially by Pick, in one of whose cases, it is true, there existed clinically an associated epilepsy.

As regards secondly, the former category of lesions, that is, the parenchymatous changes, one glance at the synopsis of the actually recognized pathological anatomy of tetany given in the

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first part of this article, suffices, to show that all the changes therein specified are abundantly illustrated in our actual observations and fully represented in the above given summary.

The lesions of the spinal cord, which we had occasion to thoroughly investigate unfortunately in one case only, exhibit in the most striking fashion, the closest analogy with those described more particularly by Bonome and Cervesato. Similarly to these observers, we found areas of parenchymatous disintegration in the central gray matter, which, in some places, had resulted in the production of actual cavities, or had been replaced by newly-formed neurogliar tissue, appearing as a meshwork of very fine, delicate and beaded fibrillæ possessing remarkably poor staining properties. These rarefied areas closely resembled in every respect the process observed in poliomyelitis, as has already been discussed. Although disseminated throughout the cord, these various changes were most pronounced in the lower cervical and in the lumbo-sacral segments; with distribution corresponds to the topography of the lesions observed in tetany. As in the case reported by Weiss, the maximum implication of the anterior horns is seen in the lower cervical segments and involves mainly the lateral cell-group, although the process does extend to the intermediate gray matter and even to the base of the posterior horn.

The lesions observed in tetany were found mainly in the spinal cord, and again more especially at the level of its cervical and lumbar enlargements; but a fact not to be forgotten and which can certainly find application in this particular instance, is, that many observers, anticipating the presence of lesions the seat of which they had based on clinical calculations, either examined the cord alone or else even limited their investigations to the cervical and lumbar regions. In the cases observed and well-described by Ferranini, the changes were most pronounced in the medulla and in the cervical cord; in the lower region of the spinal cord, they were especially prominent n the vicinity of the vesicular columns of Clarke and were often situated in territory presenting vascular disturbances. The latter details were unusually distinct in our own observations as will be remembered.

The pachymeningitis and interstitial neuritis described by Peters, were present in our Case II; mention of the former being made in the autopsy record which precedes the histologic description of this case and in which the latter lesion is more fully

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considered. As in this author's observations, the changes were found more especially in the lower cervical and upper dorsal regions; but the neuritic process was not confined to the extra-medullary segment of the spinal nerve-roots, involving the intra-medullary portion as well. It is well to state however, that in Case VII reported by Peters, extravasations in the course of the arteria spinalis anterior were observed, as well as degenerated foci in the posterior horns; lesions which were present in Case II herein reported and upon which we have dwelt sufficiently already. Peculiarly enough, as we glance over all the facts brought out by this comparative analysis, we find that the joint-lesions of our two cases include practically all the changes described in tetany by the different authors whose observations are on record.

As regards further points of comparison between the cases of tetany, which we have analyzed and our present observations, the fact should be mentioned that in two out of the seven cases reported by Peters, a marked internal hydrocephalus co-existed, and the gray matter beneath the floor of the fourth ventricle was the seat of distinct vascular changes: perivascular agglomerations of multinuclear leucocytes, even hemorrhages between ganglion-cells. Both these cases, in our opinion, can hardly be classed under the head of tetany, and we have grave doubts as to whether in these cases, the clinical manifestations were not the result of the ventricular lesions. The author states moreover, that he found by lumbar puncture an increase in the amount of cerebro-spinal fluid in most cases of tetany; a fact which we consider to be fairly good indication that choroid, that is, ventricular changes, though slight perhaps, existed.

Marfan, among others, has called attention to the peculiar tetanoid syndrome induced by internal hydrocephalus, and designated these cases by the term "tetaniform rigidity." D'Espine reported similar instances under the name of "pseudo-tetanus."

Coming back to our original proposition, namely, the ease with which the spasmodic affections, of cerebral origin, of infancy and early childhood are confounded with true tetany, which, thus far, is considered to be associated with lesions situated essentially in the spinal cord—it seems to us that the anatomic reason of this clinical difficulty has become plainly evident.

We have seen first, that the lesions described in connection with tetany, whatever diversity there existed between the different observers as regards both the seat and intensity of these

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changes, were, in almost every respect, analogous to those associated with the various forms of cerebral palsy of childhood.

In the next place, we learned that cellular and interstitial alterations absolutely similar to those ascribed to the anatomic substratum of tetany, were capable of being determined by a whole series of toxic substances, so that, the primary factor concerned in the etiology of this disease was unquestionably some poisonous principle of varying character and derivation, freely circulating in the system; a view, moreover, which is rapidly becoming universally adopted.

In order then, to fully harmonize these various facts and to substantiate our hypothesis that the anatomic mechanism of the symptom "spastic rigidity" common to both tetany and cerebral palsy in childhood, is identical in both, there remains but to show that the latter affection is itself of toxic origin, and to explain the difference (only partial however) in the topography of the lesions in the two diseases.

As regards the toxic origin of the various lesions observed in cases of cerebral palsy, it hardly seems necessary to recall: the results of the investigations of such authorities as: Strümpell, Benedikt and Vizioli, Marie, Batten, who have demonstrated that an infectious encephalitis is, in many cases, the initial underlying process; the not infrequent association of hereditary syphilis brought out by Erlenmeyer, Osler, Koenig, etc.; finally, as regards those cases whose onset is extrauterine, the so frequent occurrence of cerebral palsy following the various acute infectious diseases of childhood.

As to the divergence between tetany and cerebral palsy with regard to seat of lesion, we maintain that it is only partial, more apparent than real. The existence in the former of lesions of the brain-stem has already been referred to, and more careful and exhaustive investigation in the future will probably furnish additional instances. The changes in the nervous system in the latter affection moreover, are not confined to the brain and brain-stem; medullary lesions have been described by a number of authors. They were very distinctly present in the cases herein reported. Then, the very different circumstances under which tetany and the congenital forms, more especially, of cerebral palsy develop, must play some part in the determination of the seat of lesion; it would seem that the mere question of gravity might have some influence in localizing over the hemispheric con-

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vexity, the processes which take place during the latter months of gestation.

More important than differences in topography, are the very appreciable differences in intensity, which exist between the changes underlying the manifestations of tetany and those associated with the more severe clinical picture of cerebral palsy; and here there would be abundant room for further discussion. In attempting to explain even this major point of divergence, however, we shall confine ourselves to the following remark: if well-marked cellular and interstitial changes are produced by poisons in extra-uterine life, how much greater are not their chances of occurring in intra-uterine life, and how much more intense will they not be in the latter case, the toxic agent acting, as it does, during the very initial stage of development upon delicate struggling cells, and furthermore exercising its dwarfing influence uninterruptedly during the entire later course of gestation?

Anatomo-clinical Conclusions.

1. A large number of toxic products, whatever may be their nature and origin, are capable of producing cellular and interstitial changes in the parenchyma of the central nervous system. Many of them are susceptible of further giving rise to tetany of a more or less complete type. They do not necessarily do so, and those which most frequently are associated with the development of tetany, are not so under any or all circumstances. There is here, probably, a question of degree both in the intensity and in the duration of the irritative process, as well as one of variation in the susceptibility or resistance of the individual.

2. Tetany actually possesses probably no characteristic anatomic substratum; the lesions regarded as pathognomonic of it, merely representing the reaction of nervous parenchyma to the irritating influence of an existing toxemia. The changes may take place without determining tetanoid manifestations, just as the latter are capable of developing in the absence of any appreciable alteration of the central gray matter; which, however, is not proof positive that some changes do not exist. Our actual methods may simply be inadequate to their detection.

3. Spastic rigidity, whether symptomatic of some well-defined nervous affection or appearing as an isolated clinical manifestation, is the result, in our estimation, of a vitiated or disordered

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innervation of, or impulse-transmission to, the peripheral motor neuron; which may be dependent either (*a*) upon irritation or partial (not complete) destruction of the central motor neuron, in any part of its course from the Rolandic cortex to its point of arborization about the multipolar nerve-cells of the anterior horns of the spinal cord; or, (*b*) upon inhibition or loss of function of the cordinating centers of the spinal cord, situated in all probability (the fact not being yet proved although admitted almost universally as most probable) in the intermediate gray matter. The latter mechanism is realized in tetany, being given the seat of lesion, which, it will be remembered is in the central gray matter, involving to a greater or lesser extent the anterior horns, but never completely so. Such a lesion by destroying certain groups of cells would interfere with readjustment of stimuli, which would then react, unmodified and improperly qualified, upon the anterior motor groups. In other words, the various peripheral stimuli entering by way of the posterior nerve-roots, would be continued by means of the various reflex and other collaterals uninterruptedly into the immediate pericellular fields of the multipolar nerve-cells, and might even be intensified if the conducting collaterals traversed areas where they were subjected to irritation. Moreover, in such cases, involvement of the terminal ramifications of the central motor neuron, just previous to their contact with the multipolar nerve-cell or its dentrites, would be very easily realized. Extra-medullary or meningeal lesions may, under certain circumstances, disturb the normal transmission of impulses sufficiently to produce the same phenomenon; probably less of themselves, than on account of the secondary disturbances which they determine in the cord (compression, vascular disorders, etc.).

4. Spastic rigidity may be either very marked or very slight, with all intermediate degrees of severity; likewise, it may be either continuous or paroxysmal. In order to interpret the mechanism of production in each case, it is not necessary to invoke duality of lesion. Personally, we are of the opinion, that in its relation to variations in the severity and in the duration of the clinical symptom which it determines, the lesion exhibits directly proportionate variations both in intensity and in extent. We would readily conceive that an actual focus of myelomalacia, or a progressive sclerosis, would give rise clinically to persistent phenomena, whereas transitory vascular disorders like conges-

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tion and œdema, would produce equally transitory or paroxysmal manifestations, the repetitions of which would be as irregular in every respect as we know the underlying circulatory disturbances to be.

5. Not much lesser in importance than the meningeal localization, as a seat of lesion likely to produce spastic manifestations, is the central griseum surrounding the Sylvian aqueduct, the cavity of the fourth ventricle and the central canal of the spinal cord. The effect of irritative meningeal processes is pretty generally admitted, but the similar influence of ventricular or periventricular lesions has not yet gained, we believe, the full recognition which it deserves.

6. Internal hydrocephalus, unapparent or inappreciable clinically is not particularly uncommon in infants and young children. Why it should not in certain instances produce the characteristic enlargement of the head, when, as is often the case, the ventricular dilatation is extreme, and although the fontanelles are still open and the sutures unossified, is not clear; no plausible explanation has yet been furnished of this singular pathologic anomaly. Such cases are naturally difficult of diagnosis, and the frequent occurrence of marked optic changes and often of local manifestations as well, leads usually to the diagnosis of cerebral tumor. When this group of symptoms presents in children under one year, however, the possibility of a latent internal hydrocephalus should always be considered.

Collateral or Extrinsic Anatomic Conclusions.

1. A fair proportion of the fibres which enter into the constitution of the cerebello-olivary system take their origin from the inferior olive.

2. The constituent fibres of the brachium pontis, as could be seen from the foregoing study of an instance where this structure is absent on one side, follow a course, from above downward, which is analogous to that of the fibres of the middle segment or body of the corpus callosum. That is, they do not associate symmetrically placed territories of the pons and cerebellum.

3. Although not conclusively demonstrable simply from the actual observation, we may assume the probable existence in man of the rubro-spinal tract of von Monakow.

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4. The presence in the root-fasciculi of the auditory nerve of a certain proportion of fibres derived from the central acoustic nuclei, would seem extremely probable from the study of Case I.

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BRAIN ABSCESS IN RELATION TO SUPPURATIVE MENINGITIS, WITH REPORT OF A CASE.

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PLATE III.

INTRODUCTION.

One is somewhat surprised in looking over the literature to find what a meagre attention is given to the question of cerebral abscess in association with suppurative meningitis, this being all the more striking inasmuch as the literature of each is very voluminous. About 170 articles were analyzed for this paper and only comparatively few references to such association were found.

The case presented here having appeared to us of more interest from the standpoint of the pathology of brain abscess, we have ventured to give more consideration to this side of the literature than to that of suppurative meningitis, though the two from our analyses appear more or less inseparable. Before giving a detailed description, therefore, of this case it would seem well to briefly analyse the data which writers have contributed to this chapter of pathology.

PATHS OF INFECTION.

MacEwen emphasizes the close association of abscess with meningitis. According to his exhaustive consideration of this phase of the subject, abscess almost never occurs without some form or grade of meningitic involvement. The abscesses which result from infections of the middle ear include by far the greater number according to all authors, and MacEwen considers that seldom is there abscess resulting from this cause that does not involve the meninges in a suppurative process to some degree in its course inward. His classification of the cranial causes with their processes includes the formation of extradural abscess associated with chronic infections of the base of the skull. In this connection the question arises as to whether or not many of the cases occurring in the literature, as well as those not re-

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ported and which are recorded in the class of the suppurative meningitides, may not have been more properly placed among the cases of extradural abscess. There is a distinct process in all these cases walling off the focus of infection into the meninges with a consequent abscess or meningitis or both.

Further extension, he declares, will certainly produce leptomeningitis with superficial cerebral softening, necrosis or ulceration which is well localized. Assuming an exacerbation or fresh secondary infection at this point, there results generally a diffuse, acute leptomeningitis. Still further extension without any necessary freshening or aggravation of the infection results in more or less extensive abscess formation. He mentions also the hematogenous or idiopathic abscesses in which no path of direct extension can be traced and believes that the abscess in these cases may be formed in five different ways, namely:

1. Thrombotic extension.
2. Retrograde embolism from infected sinus thrombosis, or the "reflex method of propagation."
3. Direct extension by perivascular sheaths.
4. True infective arterial embolism or thrombosis.
5. Occlusion of a large arterial branch, with infarction.

He also adds the possibility of propagation by the lymphatics and perineural sheaths, in which latter case meningitis is most apt to be associated.

Bramwell considers in detail only the possible paths in abscess resulting from otitis and remarks that, from the general literature on the subject, they may be divided into (*a*) the small communicating veins between the ear and the petrosal and lateral sinuses and the cerebral tissue; and (*b*) the lymphatics about the blood vessels. For his own part he advances the theory that the cause is by direct extension throughout, the bone lesions causing a contiguous meningitis and this, in turn, giving rise to abscess. He, however, gives great prominence to the propagation by the venous paths as well.

Gowers mentions that external injury may cause abscess without the interposition of any secondary meningitic process, probably an intercurrent, secondary infection following hard upon the cerebral contusion, though it is most frequently propagated by way of bone lesions, meningitis, etc., by direct extension.

Uchermann's twelve cases of otitic brain abscess which yielded nine autopsies showed five cases with extension through the

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bone; three cases, two of which were cerebellar, apparently set up by infective sinus thrombosis; one case of direct extension from labyrinthine suppuration.

Miles cites a case in a man twenty-two years of age with abscess in the left temporo-sphenoidal lobe trailing off into the second and third convolutions and which was associated with a three months' otorrhea. The course of infection seemed at autopsy to be:

1. Extension to the mastoid antrum with involvement of the facial nerve.

2. Extension by the superior semicircular canal to the surface of the petrous bone and thence to the dura and cerebrum.

3. Primary involvement (abscess) of the temporal lobe.

4. Secondary abscesses extending thence to the external capsule and the lenticular nucleus.

ASSOCIATED LESIONS.

MacEwen gives in detail the lesions associated with or giving rise to abscess. He enumerates (*a*) punctured wounds penetrating the bone causing abscess by direct extension, (*b*) punctured fractures, (*c*) compound fractures with large open wounds, not likely to eventuate in abscess, (*d*) contra-coup, (*e*) infected injury without fracture extending by vascular or perivascular paths, (*f*) infective necrosis of skull without fracture, a rare condition, extending quickly by means of extra-dural abscess to subdural and cerebral abscess, (*g*) affections of the face and scalp, such as erysipelas, which seldom lead to abscess except by infective thrombosis and (*h*) middle ear lesions. Under this last heading he gives a very thorough discussion of the possibilities, probabilities and undisputed facts. He emphasizes the fact that acute affections seldom pass to the interior of the skull save when an infective thrombosis is set up, in general the chronic cases alone passing inward with an intermediate meningitis. The unfused sutures of the immature skull with the comparative ease of ingress to infection which they offer may be taken, he thinks, as an explanation of the relatively large number of individuals between the age of ten and twenty who develop cerebral abscess.

Bramwell concurs in most of these views. He mentions especially that in cases directly associated with otitis media one

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should really look back to the acute exanthem which caused the ear disease. Bramwell inclines to give much less etiologic value to punctured wounds of the brain than does MacEwen.

Gowers sums all these associations up in two classes, (1) "near" and (2) "distant." He mentions also a number of cases which occur without any demonstrable associated lesion whatever. Of 241 cases in one series, seventy per cent. are due to "near" causes and thirty per cent. equally divided between "distant" causes and cases where no associated lesion can be found. Of the "near" processes, forty-two and five-tenths per cent. are otitis, twenty-four per cent. injury and three and five-tenths per cent. diseases of the nose and orbit, non-traumatic caries, tumors, etc. Of the distant associations he places pyemia in a position of very secondary importance.

He refers to two cases[1] in the literature of association with thrush in which the organism, oidium albicans, was isolated from the abscesses. We have found one other such case[2] in the literature.

Traumatic associations in the great majority of cases occur before the age of twenty, while in pyemia the reverse holds true to even a greater extent.

Cerebellar abscess develops almost exclusively with otitis and distant sepsis.

Stoll reports five cases in which three were associated with otitis (one of which was acute), one had traumatic association and one had no association and no tangible history save indefinite cough, night sweats and expectoration.

Heimann reports that of 819 otogenous abscesses almost one-half were associated with meningitis; other most frequent complications were sinus thrombosis and extra-dural abscess.

LOCATION.

MacEwen states that the great majority of abscesses are located in the white matter and that the cerebrum is four times as often the seat of abscess as the cerebellum. With injury they are most apt to be in the frontal and parietal lobes. When associated with otitis, the seat of election is either the temporo-

[1] Ribberth, *Berl. klin. Woch.*, Vol. XVI, No. 4, Oct. 13, 1879, p. 617. Zenker, Bericht d. Gesellsch. f. Natur u. Heilk., Dresden, 1861-62.

[2] Wagner, *Jahrb. f. Kinderheilk.*, Vol. I, p. 56.

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sphenoidal lobe or the cerebellum. In pyemia they may be anywhere, but the majority of cases are in the occipital lobe. He accepts Gowers's statistics given below.

Bramwell states that seventy-five per cent. are in the cerebral hemispheres, generally in the temporo-sphenoidal lobe, and that some are located in the pons or medulla. They are somewhat more frequent in the right side. When due to ear disease they are homolateral and generally in the spheno-temporal lobe or lateral cerebellar lobe. In these cases of otitis, tympanic involvement is usually associated with abscess of the spheno-temporal lobe and mastoid or external ear disease, on the other hand, with that in the cerebellum. In pyemia abscess may be either cerebral, cerebellar or both; rarely, however, in the cerebellum alone. In trauma the abscess localizes beneath the seat of injury as a rule.

Gowers gives the most frequent location as the cerebral or cerebellar hemispheres, very rarely the pons, medulla or middle cerebellar lobe and least frequent of all the central ganglia.

Of 231 cases the locations were:

Cerebrum	186
Cerebellum	41
Pons	3
Medulla	1

In 56 cases:

	Right.	Left.
From injury	22	15
From nasal disease	7	1
From orbital disease	3	0
From caries other than in the temporal bones	1	1

Stoll's five cases showed two right and three left; two parietal, two spheno-temporal, one frontal.

Woodward reports a case of cerebellar abscess associated with persistent otorrhea. There was purulent pachymeningitis over the posterior surface of the petrous portion of the left temporal bone extending from the internal auditory meatus to the sigmoid groove. The bone under this was carious. The cerebellum where contiguous to this area was superficially soft, discolored and necrotic near the sigmoid sinus. Continuous with this area of necrosis was a large abscess cavity filled with fetid pus and bound by soft, necrotic cortical substance, the whole white matter of the entire left lobe having disintegrated.

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Heimann, from his 819 cases, concludes that abscess occurs two to three times as frequently in the cerebrum as in the cerebellum and that the seat of election is most often in the sphenotemporal lobes with the least number in the frontal, and occasionally, in the occipital either alone or with temporal involvement.

Uchermann reports twelve cases of otitic brain abscess of which six were on the left and five on the right; nine were in the temporal lobe and two in the cerebellum.

MISCELLANEOUS.

Bilrowicz, out of twelve cases, finds seven associated with otitis and five with trauma. Three of these were complicated by meningitis from the beginning.

v. Magendorf reports a case of empyema of the antrum of Highmore secondary to operation for supposed neoplasm. Autopsy revealed a circumscribed purulent meningitis with abscess of the left temporal lobe, greatly thinned cortex with a crater-like opening at the anterior extremity of the gyrus hippocampi and touching the gyrus fusiforme. In several operative cases which came to autopsy the abscesses reached nearly to the dura and in the majority the dura was either involved or was in connection with the focus of infection by means of a fistula.

Reis reports a case of panophthalmitis resulting from trauma and associated with abscess in the left frontal lobe in which the infection evidently travelled by the lymph channels.

AGE AND SEX

Abscess may occur at any age, according to Bramwell, though rarely before one year or after sixty. The majority are between ten and thirty. It is more common in males than females in as much as the former are more subject to injury. If injury be excluded sex is not a factor. It is more frequent in the laboring classes owing, probably, to this same factor.

Gowers in his series gives 174 males to 58 females.

	M		F
From otitis	2	to	1
From injury	5	to	1
From distant suppuration	4	to	1

The greater liability to abscess in males from other causes than trauma Gowers finds hard to understand.

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In 223 cases the evidence according to age is as follows:

1-9 years	24
10-19 years	48
20-29 years	72
30-39 years	29
40-49 years	26
50-59 years	16
60-69 years	7
70- years	1

One- third are in the third decade, one-fifth in the second and both together constitute over one-half of all cases.

Stoll's five cases were aged five, twenty, twenty-three, twenty-four and thirty-three. There were four males and one female.

From his series Heimann gathers that brain abscess occurs most frequently in the third decade but very rarely after sixty. He gives a proportion of only two males to one female.

Uchermann's series showed three in children and eight in adults: eight males and three females.

MULTIPLICITY.

According to MacEwen multiple abscesses are generally pyemic; when due to pyemia two-thirds of the abscesses are multiple. Ninety-three per cent. of abscesses associated with trauma are single. Eighty-seven per cent. of otogenous abscesses are single. Bramwell and Gowers consider the great majority of abscesses to be single. The latter gives four-fifths of all cases as such. He finds nearly all traumatic cases single with slightly fewer single ones from otitis. Less than one-half are single when associated with distant suppurations. One-third of pyemic abscesses are single; but it seems to be about as frequent to find two, three or many. One-half are in the same hemisphere and when in different hemispheres accompany distant septic processes only. One-fourth are in the same side of both cerebrum and cerebellum. Less frequently there are multiple abscesses in the cerebrum with more in the cerebellum.

Heimann also finds the great majority of abscesses single.

Uchermann in his series of twelve gives two multiple. One showed three abscesses in the cerebellum, the other showed two in the temporal lobe.

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PATHOLOGY AND BACTERIOLOGY.

In regard to the course of the tissue changes at the seat of abscess Gowers gives the first manifestation as one of "red softening" simply, a condition ànalogous to the stage of primary engorgement in pneumonia. Here there is no pus nor any accumulation of leucocytes for a considerable time—merely a condition of vascular engorgement with redness and softening of the cerebral tissues, due, probably, to the edema accompanying the congestion. The further progress is that of an ordinary abscess formation—the polynuclear or round-celled infiltration, the necrosis and breaking down of the tissues with the formation of pus. The contents of the abscess are usually of a greenish color and of an extremely foul odor, especially in cases of long standing. The size of the cavity varies with the chronicity and the intensity of infection. Tending to be irregular and somewhat puckered in outline in the early stages, the cavity becomes later much larger and more regularly rounded in shape.

With chronicity and in direct proportion to it, as a rule, the abscess becomes encapsulated. This occurs microscopically at about the end of the second week, is rarely distinct before the end of the third week and assumes the character of a well-defined membrane only at the end of the second month.

In regard to the organisms in these lesions MacEwen considers that any specific organism for various brain infections is a question. Certainly the same organism may produce different lesions depending on virulence, opportunities of entrance, individual resistance, etc.

Various bacteria of the naso-pharynx may enter by way of the Eustachian tube. Both pathogenic and saprophytic organisms are found in great numbers. The greatest pre-eminence is given to streptococcus pyogenes and staphylococcus pyogenes aureus. B. pyogenes foetidus and diplococcus lanceolatus have been found. Both citreus and albus were found in one case. B. meningitidis purulentæ (Eberth) has been isolated once. Pyocyaneus often accompanies the pyogenic cocci. Tubercle bacillus once accompanied aureus and pyogenes foetidus. Secondary suppurative arthritis has been caused through infection by way of the jugular vein. Oidium albicans has been isolated in three cases. This summary does not include the group of brain abscesses in which various forms of streptothrix have been found.

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Report of Case.

Clinical History.—H. P., male, nineteen years of age. Patient of Dr. W. H. George.

Family History.—Negative.

Past History.—Usual illnesses of childhood. Nothing important until one year previous to death when he suffered amputation of both legs which had been crushed in a railroad accident. Never had any ear disease or any septic process whatever during life. Habits were fair.

Present Illness.—About three weeks before his death the patient began to complain of headache and sought advice. For some time previous (length not exactly known) he had noticed exceedingly drowsy, stuporous sensations which came and went. He had felt poorly in general and his family and the attending physician noticed a decidedly marked change in temperament. He was morose, irritable and peevish. The headache was constant, very distressing and not localized. No other symptoms.

Physical Examination.—Was negative.

Clinical Course.—The patient grew slowly but steadily worse. Nausea and severe vomiting (projectile type) began and were impossible to check. The headache increased rapidly and did not respond to treatment. During the last week the patient lay in a stuporous or semi-comatose state. Several days before death the temperature rose much higher than previously and remained so until death. It had been high all through the disease. Marked retraction of head with stiffness of muscles of neck developed about this time. Convergent squint was noticed. The day before death several convulsions occurred which involved the whole body and were clonic in type as far as could be ascertained. Death followed rapidly.

Absolutely no paralysis, sensory disturbances or other localizing symptoms were noted during the disease.

Inasmuch as patient did not enter a hospital but was treated at home, the clinical record is necessarily more scanty than could be wished. The attending physician, to whose courtesy this history is due, remembers especially the astonishing lack of any suppurative process whatever which might be considered primary to the cranial conditions found at autopsy although most diligent search was made both during life and at the autopsy.

Autopsy Notes.—(Bender Laboratory Records, Autopsy No. 442), made by Dr. Blumer four and one-half hours after death, November 17, 1901.

Body of a moderately strongly built but considerably emaciated man. Both legs amputated, left at the upper third of the thigh, right at upper third of tibia. Unusual sternal prominence just above the xiphoid cartilage. Subcutaneous fat almost absent.

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The peritoneal cavity is dry. Omentum normal. Appendix passes over pelvic brim and has a mesentery to the tip. Foramen of Winslow open.

Diaphragm.—Right side, fifth rib; left side, fifth rib.

Costal Cartilages.—Not ossified.

Lungs.—Collapse on opening chest. Pleural cavities empty. What appears to be the remains of a thymus gland is present and dotted with grey nodules which do not look like tubercles.

Pericardial Cavity.—Negative.

Heart.—Negative with the exception of slight pallor of the musculature. Foramen ovale closed. Coronary arteries are normal.

Left Lung.—Bronchial glands enlarged and contain one or two calcareous nodules. No adhesions. Slight hypostatic congestion.

Right Lung.—No adhesions. Hypostatic congestion of lower lobe. A few slightly elevated areas suggestive of very early broncho-pneumonia.

Spleen.—Negative.

Liver.—Decreased in consistency. Markedly cloudy on section.

Gall-bladder.—Distended with bile. Normal in appearance.

Kidneys and Adrenals.—Negative except for well-marked cloudy swelling.

Testicles.—Negative.

Pancreas.—Negative.

Intestine.—Negative.

Head.—Scalp and calvarium normal. Convolutions plainly visible through the dura, the latter being apparently normal. Superior longitudinal sinus empty. Pia does not appear congested, but extending up the Sylvian fissure following the course of the blood vessels there is a narrow tract of purulent infiltration. On removing the brain, the pia and arachnoid are thickly infiltrated with greenish-yellow pus over the area where they envelop the crura cerebri, the pons, medulla and ventral surface of medulla. Brain not opened but hardened entire.

Cord.—Not examined.

Anatomical Diagnosis.—Purulent basal leptomeningitis of uncertain origin. Hypostatic congestion of the lungs with early hypostatic broncho-pneumonia in the right lung. Cloudy swelling of the liver and kidneys.

MACROSCOPIC DESCRIPTION OF BRAIN AFTER HARDENING.

Examination of the brain reveals in the first place the existence of a well-marked and extensive suppurative leptomeningitis involving both base and convexity, but the latter to a greater extent. The process is bilateral but is somewhat more intense on the left side. At the base, the exudate is most abundant in the domain of

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the interpeduncular space and surrounds on all sides the optic chiasm which it partly covers as a thick opaque membrane which is continued further forward and bridges over the interval between the two olfactory tracts, thus filling in the interfrontal segment of the inferior longitudinal fissure. Behind the crura cerebri, it extends slightly over the ventral surface of the Pons Varolii but especially invades the receding angle of the ponto-cerebellar junction and from there spreads over the inferior surface, margins and mesialportion of the superior surface (vermis superior) of the cerebellum. From the interpeduncular space, the exudate also extends laterally on either side, filling the fossa Sylvii and extending along the fissure Sylvii to the lateral convexity of both hemispheres. In so doing it closely follows the distribution of the Sylvian vessels but is not confined to this region, invading almost the entire convexity. Nevertheless the exudate is decidedly thicker in certain well-defined regions (*a*) over the parietal lobes, (*b*) over the motor or Rolandic areas. The frontal lobes present lesions a degree less marked. The occipital lobes are only mildly implicated and the temporal lobes as well as the mesial surfaces of the hemispheres are relatively totally free. The most abundant patch of exudate is to be found over the left hemisphere where it occurs as a very thick, broad, creamy, yellowish-white band which, starting below at the bend of the Sylvian fissure, extends almost vertically upward filling in entirely the lower half of the precentral sulcus.

Several frontal sections through the cerebral hemispheres reveal the presence of three fairly large and sharply defined, apparently encapsulated abscesses, two of which are situated in the left, the third in the right, hemisphere.

The lesions in the left hemisphere, best seen in a section passing through the pole of the temporal lobes (see Plate III, Fig. 1), occupy the deep white substance of the second and third frontal convolutions of which they destroy the basal portion (approximately the posterior one-third) of the lower two-thirds of the ascending frontal, slightly involving also, perhaps, the most anterior portion of the ascending parietal in its lower third. Both abscesses are elliptical in shape, of about the same dimensions, 4.5 centimeters by 2.5 centimeters, lying one immediately above the other and with their long axis obliquely transverse. Although in very close proximity the two abscess cavities are entirely distinct (absolutely independent). They are filled with a thick,

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Plate III

To Illustrate Drs. Archambault and Sawyer's Article on "Cerebral Abscess as an Associated Lesion in Acute Purulent Meningitis."

Albany Medical Annals, January, 1908

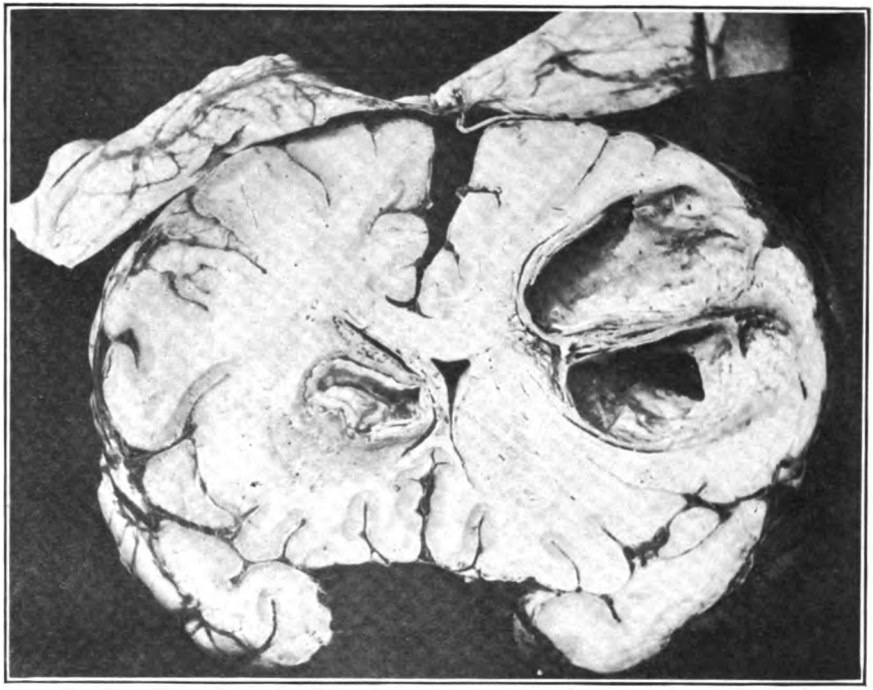

Fig. 1

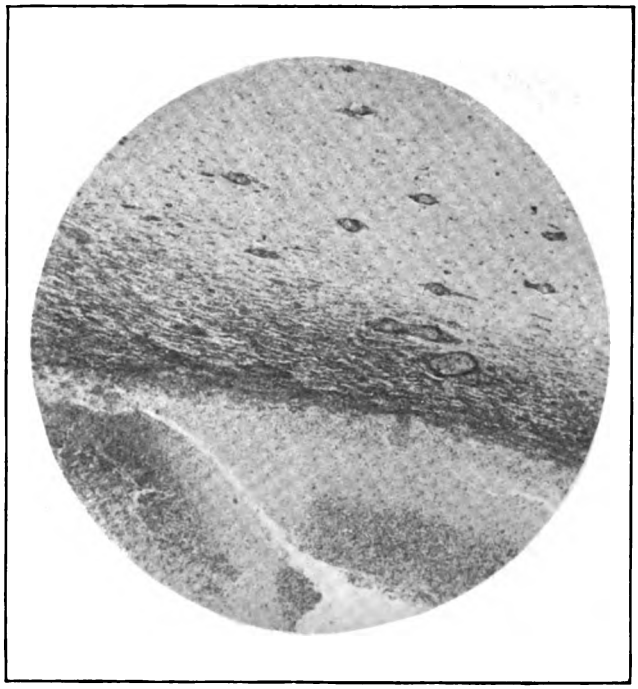

Fig. 2

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creamy necrotic substance of a greenish color and seem distinctly encapsulated by a well-defined, stratified and resistant layer. These purulent foci are confined to the centrum ovale which they have almost totally destroyed and respect entirely both the basal ganglia and the cortical substance, reaching, however, to within about one centimeter from both. More posteriorly, on a section through the genu of the external capsule, there remains but a circular cavity two by two centimeters, situated in the lower third of the ascending frontal convolution and representing simply the occipital extension of the lower of the two cavities above described. The posterior wall of the cavity is plainly visible, extending not more than one centimeter below the surface level.

The abscess situated in the right hemisphere is only visible on the section through the temporal lobes. It measures two and five-tenths centimeters by one centimeter, and its long axis is obliquely transverse. Its aspect is totally different from that of the other two owing in great part, probably, to the fact that it involves a very different kind of tissue, being almost absolutely confined to the basal ganglia. It completely destroys the head of the caudate nucleus and extends to the upper portion of the lenticular nucleus, involving as it does so a few fibres of the anterior limb of the internal capsule, the greater part of which, however, together with the lenticular nucleus, it has displaced downward and outward. The surrounding centrum ovale is very slightly, if at all, implicated. The cavity of this abscess is hardly more than a linear slit between raised and irregular borders. The general contours of the focus are far less regular than those of the two other abscesses, although a thick limiting capsule is distinctly to be seen, but it presents a puckered edge and is moreover incomplete. It is well-defined above and to the inner side but thin, jagged and interrupted below and to the outer side where the process runs off into the adjacent tissue as an irregular necrotic area which infiltrates the superior angle of the lenticular nucleus. The abscess, bulging into the lateral ventricle, fills in the space normally existing between the head of the caudate nucleus and the corpus callosum and deflects that septum pellucidum towards the opposite hemisphere. The septum pellucidum and the roof of the body of the lateral ventricle at this point do not seem intact but appear edematous and infiltrated, covered with a grayish membrane very suggestive of a purulent exudate. The

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cavity of the third ventricle is itself partly filled with a soft pulpy grayish-white material. The choroid plexuses about the foramen of Monro are slightly swollen and granular.

HISTOLOGIC DESCRIPTION.

Blocks for microscopic examination have been taken from several regions, consisting of the cortex and subcortex included between the abscess cavity and the external surface, so that the meningeal lesion, the structure of the abscess wall and the changes in its intermediate cortical gray matter could be studied.

In the first place, as regards the meningitis, it is distinctly of the purulent type. In the meshes of the pia overlying the cortical region examined, the blood vessels are, for the most part, occluded, being filled with red blood cells among which numerous black granules irregular in size and shape are disseminated and which evidently represent the products of disintegration. The vessel-wall is infiltrated with small, round cells. In the perivascular sheaths and in the meshes of the pia, exfoliated endothelial cells, abundant blood pigment both amorphous and crystalline, a few granular cells and especially polymorphonuclear leucocytes are to be seen. At several points altered and obliterated vessels penetrate into the subjacent cortical molecular zone.

The Structure of the Abscess.—The contents of the abscess cavity being partly retained are seen to consist essentially of polymorphonuclear leucocytes, many of which are disintegrated. The deeper portion of this central necrotic area is composed of large numbers of granular bodies laden with brownish granules and forming in some places two or three rows of regularly disposed cells.

From this point and extending towards the surface three distinct layers (see Plate III, Fig. 2) can be recognized, (1) the inner limiting zone, fairly broad, made up of newly formed connective tissue the cells of which are mostly of spindle-shaped variety but containing a fair proportion of matured connective tissue and through which numerous blood vessels and dense agglomerations of small, round cells are distributed; (2) the outer limiting layer less fibrillar in structure, again containing numerous blood vessels surrounded by thick agglomerations of small, round cells which are much more distinct in their morphology in this than in the preceding layer. These cells penetrate into the vessel-wall and

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also invade the adjoining parenchyma. The lumen of most vessels is occluded owing to the presence of red cells and granular bodies. In this layer regularly-disposed rows of elongated, elliptical or spindle-shaped cells, having a finely granular matrix and the nuclei of which are marginal and situated usually midway between the poles but often totally wanting, are observed; they represent very probably a modified and pathologic type of the normal glia cell (the so-called *wurstförmige Gliazellen* of the Germans); (3) more externally a third or outermost zone is to be seen which is much less well-defined and shades off into relatively normal tissue. Blood vessels become even less numerous and are no longer surrounded by dense areas of small, round cell infiltration. The typical structure of the deeper cortex can distinctly be made out in many places, although the morphologic details of most nerve cells are decidedly indistinct and their structure generally ill-differentiated. Scattered throughout the peripheral zone are fairly numerous polygonal cells, fairly large, finely granular in texture and possessing a small, centrally-placed, dot-like nucleus. They represent another pathologic variety of the glia cell and correspond to what the German have called epithelioid glia cells.

CONCLUSIONS.

Certain features of this case, finally, are worthy of especial consideration.

Regarding, first, the purulent meningitic process, it is most marked at the base of the brain, a rare situation for other than tuberculous meningitis.

The relative integrity of the temporal lobes, taken in connection with the negative findings during life and at autopsy, thoroughly excludes the possibility of the processes being otogenous in character.

With regard to the abscesses, several points of interest are to be noted. In the first place, the abscesses are multiple and limited to the cerebral hemispheres, two being on the left side and one on the right. This is in one way an unusual feature as it is generally taught that abscesses are more common in the right hemisphere, four to one, according to Gowers. As to location, two of the abscesses are strictly limited to the frontal lobes, the third one being situated for the most part in the frontal lobe

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(ascending frontal convolution) and invading the parietal lobe (ascending parietal convolution), situated for the most part in the frontal and involving the parietal to only a small extent. We have already seen that Heimann considers the frontal lobe as the least frequent seat of involvement. Then, again, the two abscesses in the left hemisphere are strictly confined to the centrum ovale. The abscess in the right hemisphere is as sharply limited, as we have seen, to the basal ganglia, destroying the greater part of the head of the caudate nucleus and the adjacent portion of the lenticular nucleus. According to Gowers this is the rarest seat of abscess formation. The case reported by Miles is the only similar one we have been able to find in the literature.

Concerning the pathogenesis of these multiple abscesses we possess practically no data upon which to base any logical course of reasoning with regard to the chronological relation they bear to the meningitis. The only facts which can be of any assistance to us are those relative to the prodromal stage of the clinical picture and which, after all, are of very uncertain significance. Still, feeling justified in according due consideration to the observations of the attending physician, according to whom these prodromata undeniably existed, it would seem reasonable to believe that these very manifestations were the clinical expression of a latent process represented by the abscess formation. Another factor which would urge strongly in favor of this hypothesis is the homolateral preponderance of both meningeal and intracerebral lesions. Even more significant than this is the fact that the most extensive area of meningitis directly overlies the point of maximum abscess development, with however this important feature, that the intervening cortex is itself in no way involved in the actual lesion. Finally, of more actual positive value than any other point thus far considered is the fact that all three abscess cavities are distinctly encapsulated by fairly mature connective tissue. Reasoning thus from this fact alone and in view of Gowers's account of the time necessary to the production of such a capsule, it appears to us perfectly justifiable to maintain that, between two lesions, one represented by a distinctly acute meningitis and the other by a stationary and definitely encapsulated process, the question of the order in which they have developed can hardly remain a matter of any grave doubt.

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THE PHYSIOLOGIC ACTION, ELIMINATION AND THERAPEUTIC APPLICATION OF SODIUM CACODYLATE, USED HYPODERMATICALLY.*

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According to Burlureaux,[1] the credit of the introduction of sodium cacodylate as a therapeutic agent belongs to Gautier, who on June 6, 1899, reported a series of observations in which he (Burlureaux) assisted. During the succeeding four years numberless enthusiastic, not to say extravagant, articles by European observers heralded the drug as a desirable substitute for metallic arsenic. On January 31, 1903, however, T. R. Fraser[2] gave the drug, so far as English and American clinicians and authors are concerned, its *coup de grâce,* for, with but one or

* Read at the Eighth Annual Meeting of the American Therapeutic Society, Washington, May 4, 6 and 7, 1907. Published also in the *Journal of the American Medical Association*, 1907, xlviii, 2090.

* Sodium cacodylate, $NaAs(CH_3)_2O_2$, is the sodium salt of cacodylic acid, $HAs(CH_3)_2O_2$. Cacodylic acid is dimethyl-arsenic acid derived from arsenic acid, $AsO(OH)_3$, by replacing two hydroxyl groups by two methyl radicles, forming $AsO(CH_3)_2OH$, also written $HAs(CH_3)_2O$.

[1] Cacodylates de Soude, *Bull. Gén. de Thérapeutique*, 1901, clxi, p. 524.

[2] The Inefficiency of the Di-Sodic-Methyl-Arsenate as a Therapeutic Agent, *The Lancet*, 1903, vol. 154, p. 304-5.

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two exceptions, all English and American text-books on materia medica deny the possibility of the drug, used hypodermatically, having either physiologic action or therapeutic value. In the article alluded to Fraser says:

"The . . . therapeutic effects of arsenic are caused by its pharmacologic action, and if it be so united with other bodies as to be incapable of producing any pharmacologic action or of inducing in large quantities the toxic effects, it can no longer be capable of producing the therapeutic effects in disease which are recognized effects of arsenic. If, therefore, the cacodylates are so inert that they may be given without producing any symptoms of the action of arsenic, it is because the arsenic has formed so firm and stable a union that no dissociating influence in the body is able to set free an arsenic ion from the combination. They are eliminated in such stable combinations that they fail to react to the tests for arsenates or yield arsenum when subjected to Marsh's test."

We are able to show that Fraser's reasoning is based on entirely false premises, for not only has it a distinct pharmacologic action (being decomposed in the body and eliminated in the form of arsenates by the urine, the feces, and probably by the sweat and the breath), and has a toxic effect, but the urine of patients under its influence yields arsenates and reacts to Marsh's test. It also gives many of the therapeutic effects common to the arsenic compounds.

The experimental part of this communication was undertaken with the view of explaining the cause of the many and excellent clinical results which have been obtained in the use of sodium cacodylate hypodermatically. An attempt was made to answer the following questions:

1. IN WHAT FORM DOES THE ARSENIC INJECTED AS SODIUM CACODYLATE BECOME ELIMINATED, AND WHAT IS THE QUANTITATIVE RELATION OF INJECTION TO EXCRETION?
2. WHAT ARE THE PATHS OF EXCRETION?
3. IS THERE A TOXIC DOSE?

In order to obtain an answer to the first question, as to the fate of the injected cacodylate, three patients were given daily hypodermatic injections of varying amounts, ranging from 0.05 gm. to 0.2 gm., and the urine examined daily.

During the time one patient was receiving 0.05 gm. for ten days no arsenic in any form could be detected in the urine.[3]

[3] Unfortunately, the value of the biologic test using *penicillium brevicaule* came to our notice too late to be taken advantage of, but we intend to employ this means of detecting in urine quantities of inorganic arsenic too small for ordinary chemical methods.

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Within twenty-four hours after commencing the second course the dose having been increased to 0.15 gm., a reaction for sodium cacodylate was obtained. Inorganic arsenic began to be eliminated after forty-four days from the commencement of the treatment, at which time the urine possessed a marked odor of garlic.

In the two other cases, in which 0.1 gm. was injected from the outset, the drug was detected on the thirty-sixth and tenth days, respectively. Inorganic arsenic could not be shown in the urine of the latter case, which was, however, under observance for only twenty-nine days. The first patient eliminated arsenic in inorganic form after twenty-two days.

Regarding the quantitative relation of the amount eliminated to that injected, our results agree in the main with those of Heffter,[4] who recovered in the urine but from one-seventh to one-ninth of the amount introduced hypodermatically. Apparently personal idiosyncrasy plays a very important part in this consideration, since in Case 3, under treatment twenty-nine days, the patient receiving daily from 0.1 gm. to 0.15 gm., only one per cent. of the injected drug was eliminated unchanged and, as previously stated, no inorganic arsenic could be detected. On the other hand, in Case 2, with the same treatment, the daily amount eliminated varied from five to eight per cent.

That these figures do not represent the true state of affairs in this connection must be evident from our results with animals. This point will be discussed later.

The question was further pursued in experiments on dogs. A detailed account of one such may serve as a type for all. Injection of 0.3 gm. of sodium cacodylate was given daily for nine days without any symptom of any objective sort. The compound was excreted on the second day and daily thereafter. On the tenth day the dose was increased to 0.5, and 1.0 gm. on the twelfth day and continued for five days subsequently. Inorganic arsenic made its appearance in the urine on the twelfth day. In a similar experiment, in which the doses were about three and one-half times the size of this one, the inorganic arsenic could be detected on the tenth day. The amount of daily elimination showed no direct relation to that of cacodylate injection. The excretion from day to day varied from 0.2 to 4 mg. In

[4] Heffter (A.): Des Verhalten der Kakodylsäure in Organismus, *Archiv. f. Experimentelle Path.*, 1901, 46, 230-241.

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general, however, the larger quantities were eliminated during the periods of high dosage. The percentage of injected sodium cacodylate eliminated varied from six to ten per cent. In all the animal experiments the injected quantity was distributed in from two to four different locations, in the attempt to determine if better results could be obtained in this way. This may explain why a lower percentage of the injected drug was eliminated. No macroscopic evidence of a pathologic change showed itself on autopsy of Dog 1. Portions of the liver, muscle and bone marrow were subjected to chemical analysis according to the method outlined by Heffter, *and in all three tissues inorganic arsenic was present.* Of especial importance was the finding in about one gram of marrow from the femur 0.3 mg. of arsenic in inorganic form. The liver showed approximately the same relative amounts with only traces in the muscle.

It occurred to us that perhaps the reason why such a small percentage of the drug could be detected in the urine after injection might be found in the fact of the elimination of the compound through the intestine in inorganic form. Ordinarily such a condition sets up intestinal changes of unpleasant character. In these experiments the feces were examined, and in all cases when inorganic arsenic began to appear in the urine it could be shown to be present in the feces also. Undoubtedly, therefore, the intestinal tract serves as a second means of exit for the inorganic arsenic formed from the cacodylate. This is only to be expected since the intestinal disturbances which follow the administration of inorganic arsenic subcutaneously are caused by the compound becoming excreted into the lumen of the intestine.

Since the injection of 3.0 gm. of the drug did not occasion any objective symptoms in the dog, it was determined to employ rabbits to show, if possible, whether or not a toxic dose could be obtained. A large rabbit, weighing 2800.0 gm., was given an injection of 1.0 gm. in the afternoon at four o'clock. The next morning the animal was found dead in the cage, but still warm. On section a very distinct odor of garlic was noticed, sufficient to be evident to persons entering the room. The tissues (liver and muscle) after removal from the animal retained the odor for several hours, or until they were subjected to chemical treatment. Arsenic in reduced form was, therefore, present in these organs. That the odor was due to inorganic arsenic was shown in the

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chemical analysis. Another rabbit, receiving 0.5 gm., showed no effect, nor did the urine possess any odor of garlic or cacodyl. The dose was increased on the succeeding day to 0.8 gm. The next morning this animal also was found dead, with the same results as with the one previously mentioned.

Our results, therefore, indicate that after the injection of sodium cacodylate from six to ten per cent. is eliminated unchanged. Arsenic in inorganic form makes its appearance in the urine and feces in small but definite amounts if the injections are continued for any length of time. In general the larger the dose the sooner the arsenic shows itself in this form. Arsenic in inorganic form also is deposited in the tissues of the body after cacodylate injection. The body, therefore, possesses the power of decomposing the organic arsenic compound into an active inorganic form. The small amount of this produced at any one time allows of large dosage without toxic effect.

This cursory summary of the experimental work thus far accomplished forms sufficient basis, we think, for the following discussion of the problem from the experimental standpoint.

In the determination of the question as to the pharmacologic value of sodium cacodylate the all-important fact to be elucidated is the possibility of the drug becoming decomposed or reduced in the animal body to cacodyl, arsenious or arsenic acid. Cacodylic acid or any of its salts unquestionably is without any great effect pharmacologically. That they may occasion toxic symptoms, however, is asserted by Lebaln,[5] Schultz[6] and Rabuteau.[7] Whether these symptoms are due to the appearance of cacodyl, which is extremely poisonous, or to the reduction of the arsenic to arsenious or arsenic acid was left undecided by those several investigators. It is currently supposed that whatever the effect of arsenic in therapeutic doses it is due to the presence of the $AsO^{2''}$ or $AsO^{3''}$ ion; in which case arsenic, combined with carbon in the so-called organic condition in which no such active ion exists, could not form a substitute for the inorganic arsenic unless it first suffered a reduction and decomposition in the tissues. That such a transformation may take place in the body

[5] *Diss. Rostock*, 1868.
[6] *Arch. f. exper. Path. u. Pharm.*, xi, p. 131.
[7] *Jahres. f. Thierchemie*, xii, p. 96.

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is too well proven by previous observers, such as Heffter, Schmidt and Chouse[8] and others, it having been shown that surviving organs *in vitro* possessed the power of decomposing cacodylic acid to the oxid or even to cacodyl itself. Such experiments did not extend to testing the products for inorganic arsenic after such treatment. Our experiments are sufficient evidence, however, to settle this point.

That such large doses are necessary to produce an effect or to get toxic symptoms is undoubtedly due to the fact of the only partial decomposition of the compound to inorganic arsenic. The extreme tolerance is to be ascribed to a self-regulation and automatic immunity which the organism attains by the constant presence and new formation of arsenic of the inorganic type. The production of inorganic arsenic in the form of arsenious or arsenic acid in *nascent* state in the body is probably not an unimportant factor in the beneficial effects obtained in arsenic treatment of this character. In this condition smaller amounts of the ion become more active and induce better results than arsenic introduced as such *per os*.

It is not, however, outside of the realm of possibility that cacodyl or its oxide, which is also unquestionably produced after this type of arsenic administration, does exert, itself, a distinct pharmacologic action specific for itself, and not unlike in general results that of inorganic arsenic compounds. This phase of the question we expect to take up as a further study.

The blood picture under the administration of the drug is a very constant one. In anemic cases there is always an increase in the percentage of hemoglobin, usually a small increase in red cells, but little variation in the number of whites, an increase in the percentage of polymorphonuclears and large mononuclears, with a corresponding decrease in the small mononuclears. In non-anemic cases there seems to be no relation in the changes of the hemoglobin or the red blood cells to the administration of the cacodylate, but there is usually an increase in the polymorphonuclears with but little change in the large or small mononuclears. The arterial pressure seems to be unaffected. The blood records in two cases, one of each type, will serve to illustrate:

[8] Moleschott's Untersuchungen, vi, p. 122.

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DATE.	Per cent. Hemo.	Red.	White.	Per cent. Poly.	Per cent. L. Mono.	Per cent. S. Mono.	Eosin. Per cent.	Dose.
March 7.....	63	4,150,000	11,500	47.5	10	37.5	4.5	0.100 Gm.
March 13.....	66	4,148,000	10,900	48.	12	36.5	3.5	0.100 Gm.
March 16.....	75	4,200,000	11,000	49.	14	36.	1.	0.100 Gm.
March 22.....	82	4,190,000	10,000	55.	18	26.	1.	0.100 Gm.
March 27.....	86	4,300,000	10,500	57.	18	24.5	0.5	0.100 Gm.
April 3.....	86	4,320,000	11,200	57.	19	23.	1.	Omitted.
April 6.....	75	4,200,000	11,300	58.	20	20.	1.5	0.150 Gm.
April 10.....	79	4,360,000	10,000	57.5	22	20.	0.5	0.150 Gm.
April 15.....	85	4,250,000	9,800	58.	22	19.5	0.5	0.150 Gm.
April 18.....	87	4,350,000	10,500	58.	23	18.	1.	0.150 Gm.

Simple anemia: blood examination made by Dr. J. Lewi Donhauser.

DATE.	Per cent. Hemo.	Red.	White.	Per cent. Poly.	Per cent. L. Mono.	Per cent. S. Mono.	Eosin. Per cent.	Dose.
Feb. 21.....	.....	5,250,000	.....	.....	.....	.....	.....	0.100 Gm.
Feb. 27.....	.....	5,240,000	6,200	58	10	30	2	0.100 Gm.
March 5.....	85	5,090,000	9,800	58	5	35	2	0.150 Gm.
March 11.....	100	6,125,000	8,600	67	1	32	0	Omitted
March 16.....	75	5,820,000	12,000	62	5	30	3	Omitted.
March 22.....	90	6,300,000	8,200	55	8	37	0	0.200 Gm
April 1.....	85	4,440,000	6,200	62	7	30	1	0.200 Gm.
April 9.....	90	4,200,000	10,400	.....	.....	.....	.....	0.200 Gm.
April 16.....	.....	5,600,000	18,000	77	6	14	3	0.200 Gm.
April 15.....	.....	5,600,000	18,000	77	6	14	3	0.200 Gm.

Neurosis; woman aged seventy-three; blood examination made by Dr. J. F. Robinson, A. B. Other blood examinations from which this report is compiled were made by Drs. A. T. Laird, C. K. Winne, Jr., and M. C. Collier, Ph.B.

In reporting the therapeutic results space does not permit giving detailed histories, but one case illustrates so forcibly the curative properties of the drug and the possibilities of large and long-continued dosage that it will be given in brief. In all instances in which the term "courses" is used it means ten days' treatment with an interval of non-treatment.

Case I.—Miss V. V., aged twenty-two, cloak model, had lichen ruber.

History.—She had been treated for eczema at varying intervals. The intestinal tract would not tolerate any form of arsenic for more than ten days. She was much emaciated and decidedly anemic (hemoglobin fifty-six per cent.) and had amenorrhea.

Treatment.—Treatment with sodium cacodylate hypodermatically commenced February 22, 1904, with 0.15 gm. once each day (this equals about 61.8 per cent. of arsenic trioxid or 0.093 gm.) for six days, when the dose was doubled. Six days later the dose was increased to 0.45 gm., and six days later to 0.6 gm. This dosage was continued for thirty-four days, when it was reduced to 0.3 gm. Four weeks later it was again reduced to 0.15 gm., and on June 15 to 0.05

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gm. every other day for three weeks, when it was omitted for ten days and then resumed for three weeks more every other day.

Result.—The patient's appetite was improved in one week after commencing treatment. She menstruated on March 15, the first time in four months, and commenced to perspire on April 15, the first in several years. She was discharged, cured, on August 4, 1904, after 164 days of treatment, having gained 25½ pounds, and she has never shown any signs of recurrence. She was given in all 41.95 gm. of sodium cacodylate, or what corresponds to 25.925 gm. of arsenic trioxid, or to 19.632 gm. of arsenic.

Three cases of psoriasis were treated. In one patient the disease was aggravated by its use and after six courses of 0.05 gm. the treatment was abandoned. Three others—one with a very severe attack—were permanently cured by four courses in one and three courses of 0.1 gm. in the others.

One patient with general eczema and one with palmar eczema were cured, the first with four courses of 0.15 gm. and the last with three courses of 0.1 gm., while a patient with eczema crurum was in no way benefited by doses as large as 0.3 gm.

Eight patients with simple anemia were successfully treated, none requiring larger doses than 0.15 gm., or more than three periods of ten days' treatment with ten days' interval.

Three patients with anemia with persistent headache were entirely cured; one of seven years' standing requiring six courses of treatment with 0.05 gm., improvement commencing during third course, and in one of six years' standing the patient was cured by four courses of 0.1 gm., improvement commencing on third day of treatment.

Three patients with splenic anemia were treated. One improved for a short time, but the cure was not permanent and the patient died. In another case, of fifteen years' standing, the patient was cured by five courses of treatment with 0.15 gm., and the third patient, a case of fourteen and one-half years' standing by the same. This patient has shown no sign of return after three years.

One patient with pernicious anemia died after eight days' treatment by a colleague, with doses of about 0.02 gm. A patient of Dr. Henry Hun, now under observation, in whom the anemia was accompanied by a persistent epistaxis of several years' standing, shows marked improvement, the fever, delirium, dyspnea, epistaxis and other disagreeable symptoms having disappeared, the hemoglobin having increased from 20 to 40 per cent., and the red cells from 1,032,000 to 2,400,000 in twenty-seven days with doses of 0.06 gm. for twelve days, 0.12 gm. for eight days, and 0.15 gm. the balance, and at which doses the man is still being treated.

One patient with Hodgkin's disease died. This case was treated at our suggestion by a colleague, and no history is obtainable.

Two patients with neuritis with anemia were cured with 0.05 gm. doses, one after three courses of ten days, and the other after two courses. In another case, in which there was no associated anemia, there was no improvement.

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Two patients with chorea were successfully treated by the administration of 0.1 gm. for two and three courses, respectively, one had been treated for some time with liquor potassii arsenitis, and, while benefited, was never cured, as the attacks recurred at three months intervals.

One patient with gastralgia of malarial origin was cured by two courses of 0.15 gm., and in two cases of exhaustion—both in women of more than 60 years, one following bronchitis and one following what was called diabetes — the patients were speedily helped to a complete recovery.

Of neuroses of various character, sixteen were treated, in only two cases more than 0.15 gm. being used. Five of these patients were not benefited, four were much helped and seven were cured.

Of forty-five cases reported then, thirty-four patients were either entirely cured or much benefited, eleven were in no way helped, and two were apparently made worse. In several of the second class the failure may be due to the fact that they were among the earlier cases treated, the dosage being very small and there being certain faults in technic. In these cases a French preparation sold in tubes, each containing a solution representing 0.05 gm., were used subcutaneously, with a short needle, the solution being cold. Later a sterile solution was made by dissolving the salt in distilled water. This, however, soon developed fungi, and on boiling gave off an alliaceous odor. Our present practice is to obtain the required amount of the salt, each dose enclosed in a gelatin capsule by the pharmacist; the drug is poured into the open end of a glass syringe, the plunger replaced and the syringe then filled with boiling water; the site of injection, preferably the buttock, is then washed with alcohol and a long needle is thrust deeply into the gluteal muscle and the warm solution injected. By this method little if any discomfort is complained of, and the warmth of the solution seems to add much to the rapidity of effect. Clinically it is usually noted that soon after injection there is a marked sense of exhilaration, and it is no unusual thing for a patient to come back after the cessation of a course and request a resumption of treatment on the ground that "it makes me feel so much better," a symptom common to arsenic medication.

Almost invariably the patient gains in weight, usually with considerable rapidity at first. In three of our cases a marked garlic-like odor to the breath was observed, in one this invariably coming on in half an hour after an injection of 0.05 gm. One patient

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reported the odor in the perspiration about a week after injections of 0.2 gm. commenced, and a complaint of a garlic odor to the urine is no infrequent occurrence. This odor may also be observed in inorganic arsenic medication.

Many of the French writers state that unless improvement commences after five or six injections it is not worth while to continue, and if one course has not proved beneficial a second is not likely to. Our experience, however, is that rapidity of improvement depends much on the size of the dose, being slow with small doses and quick with large ones.

It would seem, therefore—if our data be accepted as correct—that Fraser and those who have accepted his statements have (as Fraser's paper seems to indicate) made their sweeping assertions as the result of a few clinical failures and not as the result of careful physiologic observation.

CONGENITAL STENOSIS OF THE DUODENUM.—REPORT OF CASE.*

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AND

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Instructor in Pathology and Bacteriology, Albany Medical College.

PLATE IV.

Congenital occlusion of the intestine is an infrequent condition. Theremin, in 1877, emphasizing its rarity, states that among 111,401 children this malformation was observed only twice, and in St. Petersburg it had occurred but nine times. At that time no cases had been reported from the foundling asylums in Moscow and Prague. In 1883, Gärtner collected thirty-eight cases; in twenty of these the occlusion had occurred in the jejunum and ileum, in sixteen in the duodenum and twice in the colon. Cordes, in 1901, collected fifty-six cases of duodenal occlusion and added one observation of her own. In 1903, Kuliga, after a very careful search through the literature, succeeded in bringing together 185 cases, forty-six of which occurred in the duodenum, ninety-four in the jejunum and ileum and forty-five in the colon and rectum.

* Published also in *Archives of Pediatrics*, 1907, XXIV, 813.

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The following case, aside from its rarity, is of interest, as the condition was recognized clinically.

Mrs. C., of Williamstown, Mass., came to Albany for her confinement because she wished her baby to be under the care of a specialist, and was referred by Dr. Snow, of Buffalo, to the writer (Dr. Shaw). In my absence from the country Dr. MacFarlane, of Albany, took charge of the patient, and to him I am indebted for the notes and history of the case.

Clinical History.—The child, a girl, was born July 19, 1906, at 9:50 P. M., at the Albany Hospital, under the care of Dr. Macfarlane. The labor was normal, except for a retained placenta and some postpartum hemorrhage, and the mother made an uninterrupted recovery. The child seemed strong and healthy and weighed seven and one-half pounds. Twelve hours after birth she passed meconium. She was given small quantities of warm water and vomited a small amount of greenish fluid fifteen hours after birth. She was placed at the breast two hours later and again in two hours, and after the latter feeding vomited a small quantity of greenish fluid which contained particles of a white material evidently milk curds. The next nursing was retained. On the next two days (the second and third after birth) she nursed at the breast; vomited greenish fluid five times, once in large quantity; passed meconium three times; seemed hungry and cried as if in great pain. On July 23d (the fourth day after birth) it was thought that the nervous state of the mother might be responsible for the condition of the child. Nursing at the breast was discontinued and barley water and, later, whey was administered. A greenish-yellow fluid containing white particles was vomited almost immediately after each ingestion of food. Meconium was passed and later a brownish movement showing a small amount of mucus. On July 24th (the fifth day after birth) hot water was given in dram doses every hour, and retained at the longest only twenty minutes. The stomach was thoroughly washed out after the removal of putrid, foul-smelling greenish contents. During the night there were three small brownish dejections. On the sixth day after birth (July 25th) the stomach was washed out twice and the child vomited only once (a clear fluid two hours after the last lavage). A napkin and some of the vomited material were examined by Dr. H. C. Jackson, of the Bender Laboratory, and bile was shown to be present in both.

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Dr. Albert Vander Veer was then called in consultation. On account of the apparent improvement in the gastric condition, and the fact that bile had been found in both vomitus and dejection, it was hoped that the stenosis might be spastic, and operative intervention was postponed. On the next three days the stomach was washed daily, whey was given by mouth and normal saline solution per rectum three times a day. Although she vomited only once in these three days, she grew constantly weaker, and on July 29th, ten days after birth, she weighed five and one-quarter pounds, showing a loss of two and one-quarter pounds. Her condition gradually grew worse in spite of lavage, and an operation having been deemed unadvisable on account of her exhausted state, she died on August 1st, thirteen days after birth.

Autopsy Record (Bender Laboratory 0-1,028).—Postmortem examination made August 3, 1906, by Dr. Baldauf.

Clinical Diagnosis.—Stenosis of the intestine below and near the opening of the common bile duct.

Abdomen.—Subcutaneous fat almost absent. Peritoneal surface smooth and glistening. Spleen not enlarged, free from adhesions. Appendix, coiled upon itself and retrocecal, measures about 3 cm. in length. Mesenteric lymph nodes somewhat enlarged, pale and firm. Below the pyloric orifice of the stomach is a dilatation of the intestine including the whole course of the duodenum and extending below the bile duct, giving the organ, from its size and general shape, the appearance of the stomach. The mesocolon of the entire ascending colon, except a small free edge about 0.5 cm. in thickness, is intimately adherent to the dilated duodenum.

Measurements.—Circumference of pyloric orifice, 2.2 cm.; length of small curvature of the stomach, 5.8 cm.; length of greater curvature of the stomach, 16.2 cm.; circumference of the dilated duodenum, 1 cm. from the pylorus, 3.7 cm.; circumference of the dilated duodenum, 2 cm. from the plyorus, 4.8 cm.; length along the greater curvature of the dilated duodenum, 18.5 cm.; length along the lesser curvature of the dilated duodenum, 9 cm. The stricture lies 5 cm. below the papilla of Vater. The greatest diameter of the dilated duodenum is 9.4 cm.

Below the dilatation is a stricture which will not admit the smallest probe, but through which small amounts of fecal material can be forced.

All other organs normal.

Anatomical Diagnosis.—Congenital duodenal stenosis.

Various causes have been assigned as etiological factors in these congenital anomalies. Until very recently no satisfactory

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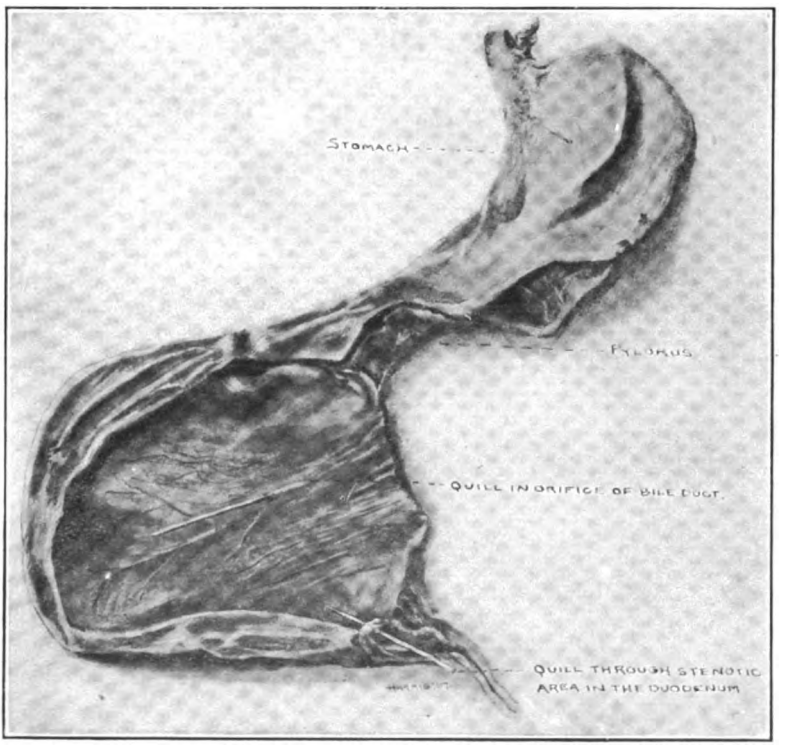
Plate IV

To Illustrate Drs. Shaw and Baldauf's Article on "Congenital Stenosis of the Duodenum; Report of a Case."

Albany Medical Annals, January, 1908



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explanation has been offered for the larger number of the cases. In many instances associated pathological lesions were considered, but when such did not exist there was recourse only to hypothesis and theory. Silbermann, Theremin and Fiedler have suggested the idea of peritonitis during fetal life as a causative factor. Fiedler does not consider that the absence of any evidence of peritonitis is proof positive that a peritonitis has never existed, for he maintains that a peritonitis may have disappeared without leaving any trace of the original lesion. Such peritonitis is generally of syphilitic or tuberculous origin. According to some authors, the peritonitis must have existed before the third month, because, in the cases examined, where there was total occlusion of the intestinal lumen, no bile appeared in the distal portion of the gut. Where the syphilitic condition existed so early and the child went to normal delivery, it seems strange that no other signs of syphilis were visible, for in the cases examined no visceral changes were evident. Mauclaire's case, in which he ascribes the occlusion to a tuberculous peritonitis, may have been the result of the volvulus which was present, the tuberculous peritonitis being secondary. This is the view of Schottelius. Küttner, Gärtner, Schottelius, Schlagel and Good believe the condition to be the result of volvulus. A few cases have recently been added to the thirteen cases due to volvulus collected by Gärtner. There are some, however, who consider the volvulus secondary to other conditions. Steinthal, Kirchner, Marchwald and others consider the atresias and stenoses part of an intrauterine enteritis. Marchwald, in one of his cases, demonstrated cocci at the seat of the lesion. In a case reported by Chiari, an intussusception was demonstrated. Pressure from without is considered of importance by others; for instance, in a case reported by Wiederhofer an alveolar carcinoma involving the liver was found, in Kristeller's case an enlarged liver, in Hirschsprung's and Serr's case a hypertrophic head of the pancreas, in Schott's case a cyst of the ileocecal fossa, in Nobiling's case formation of a loop by the omphalomesenteric artery. As other factors, Jacobi and Charrier laid stress on the formation of amniotic bands pressing and occluding the gut. Hess emphasized the possibility of compression of the duodenum at the point where it pierces the mesocolon. Wyss and Hammer think the stenosis is due to hypertrophic valvulæ conniventes, and Bretschneider, Hempel, Schellong and Ahlfeld ascribe an influence

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to the omphalo-mesenteric duct. While these various influences may be of some interest in the production of these anatomical lesions and the various hypotheses and theories may apply to a certain number of cases, there are numerous cases for which no cause is evident and no logical hypothesis can be offered. An hypothesis which might apply to all cases could be formulated on a purely embryonic basis. Tandler, in a recent communication, emphasizes the transitory disappearance of the lumen of the intestine in the earliest embryos. In studying the cross sections of the duodenum of a 12.5 and 14.5 millimeter embryo, he observed the lumen occluded by an epithelial-like proliferation. He afterward made a systematic examination of eleven embryos ranging from thirty to sixty days old. In the two youngest embryos the duodenum was visible with an open and unobstructed lumen. In the next older an increase of the epithelial elements had begun with evident narrowing of the lumen, while in the next two older embryos the increase of epithelial cells and narrowing of the lumen were more evident. This became more marked in the next older embryo, while in the three oldest embryos there was a disappearance of the epithelial cells and the intestine had assumed its original appearance. To summarize: In the youngest embryos the lumen of the intestine was easily visible, but later the lumen disappeared on account of a proliferation of epithelial cells. Later, however, the epithelial cells became absorbed and the lumen reappeared. If these observations be accepted, we may find an explanation of many cases of atresia and stenosis; the atresia being dependent upon the non-absorption of the hyperplastic epithelium and the stenosis upon its partial absorption.

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LIPOMA OF THE INTESTINE OCCURRING IN A CHILD THIRTEEN MONTHS OLD AND CAUSING SYMPTOMS OF INTESTINAL OBSTRUCTION.*

By GEORGE CHANDLER, M.D.,
Of Kingston, N. Y.

AND

LEON K. BALDAUF, M.D.,
Instructor in Pathology and Bacteriology, Albany Medical College.

Lipoma, as an intestinal tumor, occurs very infrequently. Hiller in 1899 collected twenty-three cases. A later review by Ward, including the cases reported by him, increased the number to thirty-five and in a recent very comprehensive review, Dewis has added nine additional reports. The rarity of the lesion, the early age at which it appeared in the case here given, the peculiar symptoms to which it gave rise and the fact that the literature contains no reference to a similar condition in an infant, makes the following report worthy of publication.

Clinical History.—Female, aged thirteen months, appeared for operation September 13, 1906, with symptoms of intestinal obstruction.

Family History.—Negative.

Past History.—The child was born July 12, 1905, after a normal labor. It was breast fed and appeared well nourished at first but later showed slight signs of rickets. Two or three months after birth, the mother noticed that the left side of the abdomen appeared unusually full and round. She attributed this, however, to the healthy condition of the child. At that time there were no stomach symptoms, but a slight "colic" appeared which continued daily for four or five months. The attacks later however diminished in frequency, there being intervals of two or three weeks, during which the child appeared perfectly well. Defecation has always occurred two or three times a day. The feces were soft in consistency; well formed stools have never been seen.

Present illness began July 15, with vomiting and marked flatus. Rectal enemata were given and afforded complete relief. The child then remained well until August 7 when she had a similar attack, the same treatment again proving effective. During these attacks the mother noticed a "bunch" in the left side of the abdomen, which remained after the attacks had subsided. The child had similar attacks on August 20 and 30. On September 9 continuous vomiting developed and marked constipation which nothing could relieve. The patient became steadily worse and was brought to the Benedictine Sanitarium in Kingston, N. Y., September 13, 1906. At this time the child was

* Published also in *Annals of Surgery*, 1907, xlv, 836.

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in a precarious condition; the pulse was barely perceptible; the abdomen markedly distended and vomiting continuous.

Operation.—Ether anesthesia. Incision in the median line. Removal of a large pedunculated tumor occupying the right portion of the abdominal cavity and attached to the sigmoid flexure opposite the mesenteric attachment by a short pedicle 10 cm. in length. The tumor had rotated in such a way that the intestine was twisted twice. The tumor was removed by cutting the pedicle close to the intestinal wall. The child made an uneventful recovery and left the sanitarium two weeks later.

Pathological Examination.—The specimen consists of a kidney-shaped mass 12 x 7 x 9 cm. with a broad pedicle attached to the concave side or "hilum." The surface is everywhere smooth and glistening. Beneath the surface are numerous hemorrhagic areas averaging 2.5 cm. in the greatest diameter. At the point of attachment, the mass is definitely lobulated. On section, the yellow tissue is mottled with numerous hemorrhagic areas, which are especially abundant at one pole of the tumor. The tumor substance shows in places a division by fine strands of connective tissue into definite and rather large lobules. Elsewhere it presents a lamellated appearance, no lobules being visible. The mass is rather elastic in consistency and on pressure a fatty material is expressed. Microscopic examination reveals a pure lipoma with areas of hemorrhage.

Anatomical Diagnosis.—Lipoma with numerous areas of hemorrhage.

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DEWIS, J.‖W. A Small Fibroma of the Ileum resulting in Obstruction of the Bowel, with a Consideration of Various Forms of Benign Intestinal Tumor. *Boston Medical and Surgical Journal*, 1906, CLV, 427.

RUPTURE OF UTERUS DUE TO A FIBROMYOMA.

BY WM. A. KRIEGER, M.D.,
Pathological House-Officer to the Albany Hospital.

Rupture of the uterus may take place from a variety of causes, as external violence, blows, falls or kicks. It may rupture from internal traumatisms as from the application of forceps, attempts at version or the introduction of a hand into the uterus or by vehement muscular efforts to overcome some disparity between "passage and passenger" as by malpresentation, hydrocephalus, spina bifida, sacrococcygeal tumors, rigid os, contracted pelvis, tumors of pelvis and cicatrices, in which cases it is usually transverse through the lower segment. Or it may lacerate because

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of some disease of the organ itself as interstitial pregnancy, bicornuate uterus, degeneration of the muscle, scars after Caeserian section, or rarely, tumors such as carcinoma and myomata. In the following case, for the privilege of reporting which, I am indebted to Dr. G. C. Madill, of Ogdensburgh, N. Y., we have to deal with the latter condition.

Clinical Notes.

Mrs. M., twenty-six years of age, housewife.

Past History.—Patient has been married 5 years, but has never been pregnant. Menstruation has been regular but rather excessive. During the Fall of 1906 she had an attack of severe pain and some uterine hemorrhage and was ill for two weeks. From that time to present illness has been apparently perfectly well.

Present Illness.—July 8, 1907, she began to have pain in the lower abdominal region. During the night of July 8, she was taken with severe pain in the abdomen, vomiting and faintness. When patient was seen she showed every evidence of peritoneal hemorrhage and was advised to enter the hospital. On entering hospital patient was in the condition of shock.

Laparatomy was immediately performed. The abdomen contained a large quantity of blood and a tumor was found partially extruded from a rent in the wall of the uterus. The tumor was removed and the uterus amputated above the cervix. Patient made an uneventful recovery and was discharged from the hospital July 27, 1907.

Pathological Report.—The material for examination consists of two masses, one a uterus the other a tumor mass.

The tumor mass is roughly spheroidal measuring 12 x 10 cm., has no capsule, is somewhat coarsely lobulated, exceedingly firm and reddish gray in color. In the center there is a cavity, the result of cystic transformation. The cut surface presents a grayish smooth, glistening, translucent surface outlined here and there by denser fibrous areas. In places it shows necrosis and hemorrhage.

The uterus is greatly distorted; the only portion normal is the fundus to which are attached on either side the Fallopian tubes. These are cut short and the ovaries are not present. Uterus measures 8 cm. in length and 5 cm. across the fundus. The thickness of the wall at the fundus is about normal. The remainder of the wall is transformed into a thin fibrous membrane which in places is so thin that it is transparent and is freely torn. The outer surface shows a few adhesions. The inner surface is marked by an irregular interlacing network of fibrous tissue and muscle bundles. In several places this thinning of the wall involves the cervix which as such cannot be recognized. The mucosa which remains is transformed into a smooth, glistening membrane with small polypoid protuberances.

Microscopic examination of the tumor shows that it is composed of bands of smooth muscle and connective tissue coursing in various

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directions, the muscular tissue in parts being cellular and deep-staining. Throughout the tissue extensive necrosis is present.

Anatomical Diagnosis.—Fibromyoma of uterus causing thinning of uterine wall and rupture.

It is not a simple matter to explain the sequence of events which led to the rupture of the uterus, but it would appear to be due to a thinning of the uterine wall (a pressure atrophy) caused by the pressure of a large, apparently submucous, myoma interfering with the blood supply. A careful review of the literature of rupture of the uterus as presented by the Index Medicus and the catalogue of the Surgeon-General Library fails to reveal a similar case.

BENDER HYGIENIC LABORATORY.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1907.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1907.

The Work of the Laboratory.—The routine examinations of all kinds are summarized in the following table:

ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1906, TO AUGUST 31, 1907.

	Albany Hospital.	St. Peter's Hospital.	Child's Hospital and St. Margaret's House.	State Department of Health.	City Board of Health.	All Other Sources.	Totals.
Autopsies	36	4	17	.....	.....	78	135
Surgical Specimens	1,071	372	20	.....	.....	154	1,617
General Bacteriology & Clinical Microscopy	85	45	2	2,170	3,126	297	5,725
Totals	1,192	421	39	2,170	3,126	529	7,477

The only important change in our routine work has been the withdrawal of the water examinations for the State Department of Health. These are now made by the State Hygienic Laboratory. In place of this work we give two courses of instruction

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in bacteriology to such health officers of the State as care to attend. These courses are given twice a year, each course covering a period of one week.

Laboratory courses for undergraduates of the Albany Medical College have been given as follows:

1. *Normal Histology.*—Drs. Beilby and Douglas, six hours a week.

2. *Pathology and Bacteriology.*—Drs. Pearce, Baldauf, Schaible, Robinson and Hacker, seven and a half hours a week.

3. *Clinical Microscopy.*—Drs. Laird and Rulison, two and a half hours a week.

4. *Surgical Pathology.*—Drs. Elting, Carey and Sibley, two and a half hours a week.

5. *Histology and Pathology, in connection with the course in Obstetrics.*—Drs. Lipes and Douglas, two and a half hours a week.

6. *Anatomy and Pathology of the Nervous System.*—Dr. Archambault, two and a half hours a week.

7. *Experimental Physiology* (*Second year*).—Dr. Jackson, four hours a week.

8. *Demonstrations in Physiology* (*First year*).—Dr. Becker, two hours a week.

It will be seen that the only changes have been the introduction in the first and second years, of courses in experimental physiology under the direction of Drs. H. C. Jackson and E. W. Becker.

Among those who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are Dr. H. S. Rowe of Ballston, Drs. W. L. Huggins and S. S. Ham of Schenectady, Drs. A. H. Traver, W. H. Kelly and H. P. Carpenter of Albany, Messrs. J. L. Donhauser, E. E. Tredway, S. Friedman, R. P. Harris, E. S. Haswell, Nelson Fromm, W. H. Davidson and E. W. Jackson of the Albany Medical College. These have assisted in the routine work of the laboratory, pursued special lines of study or engaged in research work.

Investigations completed during the year are as follows:

1. Dawes, S. L., and Jackson, H. C., The Physiologic Action, Elimination and Therapeutic Application of Sodium Cacodylate Used Hypodermatically. *Journal of the American Medical Association,* 1907, XLVIII, 2090.

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2. Baldauf, L. K., An Investigation of the Nature of Proteid-Soap Compounds and of the Micro-chemical Staining of Pure Fats and Lipoids by Scharlach R and Sudan III. *Journal of the American Medical Association*, 1907, XLIX, 642.

3. Chandler, G., and Baldauf, L. K., Lipoma of the Intestine Occurring in a Child Thirteen Months Old and Causing Symptoms of Intestinal Obstruction. *Annals of Surgery*, 1907, XLV, 836.

4. Jackson, H. C., and Pearce, R. M., Experimental Liver Necrosis. I. Hexon Bases. *Journal of Experimental Medicine* (in press).

5. Pearce, R. M., and Jackson, H. C., Experimental Liver Necrosis. II. Enzymes. *Journal of Experimental Medicine* (in press).

6. Pearce, R. M., and Jackson, H. C., Experimental Liver Necrosis. III. Nitrogenous Metabolism. *Journal of Experimental Medicine* (in press).

7. Jackson, H. C., and Pearce, R. M., Experimental Liver Necrosis. IV. Nuclein Metabolism. *Journal of Experimental Medicine* (in press).

8. Jackson, H. C., and Pearce, R. M., Experimental Liver Necrosis. V. Fats and Lipoids. *Journal of Experimental Medicine* (in press).

9. Archambault, L., The Inferior Longitudinal Bundle and Geniculo-Calcarine Fasciculus with Remarks on the Stratum Sagitalle Extremum Temporo-occipitale. (Publication deferred.)

10. Archambault, L., and Baldauf, L. K., A contribution to the Pathogeny of Spastic Rigidity of Childhood. ALBANY MEDICAL ANNALS (in press).

11. Archambault, L., and Sawyer, H. P., Cerebral Abscess as an Associated Lesion in Acute Purulent Meningitis. ALBANY MEDICAL ANNALS (in press).

12. Shaw, H. L. K., and Baldauf, L. K., Congenital Stenosis of the Duodenum; Report of a Case. *Archives of Pediatrics* (in press).

13. Hacker, C. W. L., Concerning the Appearance of Glycuronic Acid in Certain Conditions of Diminished Oxidation. (Publication deferred).

Of these investigations, the fourth to eighth, inclusive, were conducted under grants from the Rockefeller Institute for Medi-

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cal Research; the second and thirteenth under grants from the Committee on Scientific Investigation of the American Medical Association, and the greater portion of the expense of the investigations in Neuro-pathology was met by Dr. Henry Hun.

Changes in the Staff.—Dr. L. K. Baldauf resigned June 1st to accept a position as Assistant City Pathologist of St. Louis, Mo., and in his stead has been appointed Harold Paine Sawyer (B. S., Univ. of Alabama, 1902; M. D., Johns Hopkins Medical School, 1906). Dr. Frank George Schaible resigned July 1st in order to become Assistant in the Clinical Laboratories of the Manhattan State Hospital, Ward's Island, N. Y., and has been succeeded by Clinton Benjamin Hawn (B. S., Union University, 1903; M. D., Albany Medical College, 1906). Dr. Fletcher Robinson resigned June 1st in order to become Pathologist to the Mercy Hospital, Pittsburg, Pa., and was succeeded by C. W. L. Hacker (M. D., Albany Medical College, 1905), who for the past year has been connected with the laboratory as Pathological House Officer to the Albany Hospital. To this latter position for the year ending June 30, 1908, William Andrew Krieger (M. D., Albany Medical College, 1906) has been appointed by the Board of Governors of the Hospital.

I wish here to express my appreciation of the great benefit to the laboratory of the assistantship in neuro-pathology supported by Dr. Henry Hun, and of the two assistantships in surgical pathology supported by Drs. Albert Vander Veer, W. G. Macdonald and Arthur W. Elting. To one of the latter positions, newly created, has been appointed Dr. T. Frederick Doescher (M. D., Albany Medical College, 1906.)

I wish also to express my appreciation of the services of Dr. J. Lewi Donhauser who for the greater part of the year acted as voluntary assistant and who has recently been appointed Resident Pathologist to the Pennsylvania Hospital of Philadelphia.

Mr. George Edward Willcomb, S. B., continues as Assistant Chemist and Bacteriologist in charge of the Albany Filtration Plant.

Improvements.—Aside from necessary repairs the only important changes have been the installation of a projection lantern and the proper curtaining of the lecture room for the use of the same.

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The Bender Laboratory Club.—This organization, now in its third year, has continued most active. The guests during the past year were Dr. Eugene L. Opie of the Rockefeller Institute for Medical Research, New York, who presented a review of his work on the "Enzymes of Phagocytic Cells in Inflammatory Conditions," and Dr. David L. Edsall, Assistant Professor of Medicine at the University of Pennsylvania, who discussed "Occupational Poisonings."

Respectfully submitted,

RICHARD M. PEARCE,

Director.

October 1, 1907.

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STUDIES

FROM

THE BENDER

HYGIENIC LABORATORY

ALBANY, N. Y.

REPRINTS

VOLUME V

1908

FORT ORANGE PRESS
BRANDOW PRINTING COMPANY
ALBANY, N. Y.

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NOTE.

THIS volume comprises the publications of the Bender Hygienic Laboratory for the year 1907-'08. Some of these have appeared elsewhere, but for the sake of uniformity have been reprinted from the Bender Laboratory Number (January, 1909) of the ALBANY MEDICAL ANNALS. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE.

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STUDIES

FROM

THE BENDER

Hygienic Laboratory

ALBANY, N. Y.

REPRINTS

Volume V

1908

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The Bender Hygienic Laboratory

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GEORGE E. GORHAM, M. D. (Sec'y) HARRY H. BENDER (Pres.)
WILLIS G. TUCKER, M. D.

Staff

(*For the Year Ending August 31, 1908*)

RICHARD M. PEARCE, M. D., *Director*
(*Resigned August 31, 1908.*)

HOLMES C. JACKSON, Ph. D., *Physiological Chemistry*

H. P. SAWYER, M. D., *Pathology*
(*Resigned August 31, 1908.*)

C. B. HAWN, M. D., *Bacteriology*
(*Resigned August 31, 1908.*)

LA SALLE ARCHAMBAULT, M. D., *Neuro-pathology*

C. W. L. HACKER, M. D., *Surgical Pathology*
(*Resigned May 31, 1908.*)

T. F. DOESCHER, M. D., *Surgical Pathology*
(*Resigned June 30, 1908.*)

J. L. BENDELL, M. D., *Surgical Pathology*
(*Appointed June 1, 1908.*)

L. H. GAUS, M. D., *Surgical Pathology*
(*Appointed August 1, 1908.*)

E. J. BUCHAN, M. D., *Volunteer Assistant*
(*Resigned August 31, 1908.*)

Pathological House-Officer

(*Appointed by the Governors of the Albany Hospital*)
WM. A. KRIEGER, M. D.
(*Resigned June 30, 1908.*)
R. C. KEIGHER, M. D.
(*Appointed July 1, 1908.*)

Assistant Chemist and Bacteriologist
(*In Charge of the Albany Filtration Plant*)
GEORGE E. WILLCOMB, S. B.

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Laboratory Courses of the Albany Medical College

(Given in the Bender Laboratory)

Session of 1907-'08.

Pathology and Bacteriology

RICHARD M. PEARCE, M. D., *Professor of Pathology and Bacteriology*
H. P. SAWYER, M. D., *Instructor in Pathology and Bacteriology*
C. B. HAWN, M. D., *Instructor in Pathology and Bacteriology*
T. F. DOESCHER, M. D., *Instructor in Pathology and Bacteriology*

Histology

GEORGE E. BEILBY, M. D., *Lecturer on Histology*
MALCOLM DOUGLAS, M. D., *Instructor in Histology*

Surgical Pathology

ARTHUR W. ELTING, M. D., *Lecturer on Surgical Pathology*
C. W. L. HACKER, M. D., *Instructor in Surgical Pathology*
EDWIN F. SIBLEY, M. D., *Instructor in Surgical Pathology*

Clinical Microscopy

ARTHUR T. LAIRD, M. D., *Lecturer on Clinical Microscopy*
(On leave of absence.)
HARRY RULISON, M. D., *Instructor in Clinical Microscopy*

Anatomy and Pathology of the Nervous System

LA SALLE ARCHAMBAULT, M. D., *Lecturer on Neurology*

Anatomy and Pathology of Obstetrics

H. JUDSON LIPES, M. D., *Clinical Professor of Obstetrics*
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RICHARD M. PEARCE, M. D.

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Richard M. Pearce, M. D.

Director 1903-1908

Dr. Richard M. Pearce was appointed director of the Bender Hygienic Laboratory, September 1, 1903. Leaving his position with the pathological department of the University of Pennsylvania, Dr. Pearce came to Albany and began at once what proved to be a most successful and satisfactory work. In the Albany Medical College he became an able and efficient teacher of pathology, bacteriology and histology and was elected to full professorship after his first year, which position he held with credit to the Medical College and honor to himself until his resignation, September 1, 1908. The contract work done by the laboratory under Dr. Pearce for the State of New York and the city of Albany in the examinations of water, blood, sputum, cultures, etc., was well and promptly done and gave entire satisfaction. In addition to the teaching, state and city work, autopsies and pathological work, Dr. Pearce carried on an independent line of research work, much of which was published and is a distinct contribution to scientific medicine. The marked business ability and executive skill of Dr. Pearce contributed much to the financial success of the laboratory during his directorship.

As evidence of their high appreciation of his sterling worth, this minute is hereby inscribed by the Trustees of the Bender Hygienic Laboratory.

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Original Communications

THE APPEARANCE OF GLYCURONIC ACID IN CERTAIN CONDITIONS OF DIMINISHED OXIDATION.*

By C. W. LOUIS HACKER, M. D.

Instructor in Surgical Pathology, Albany Medical College.

Considerable scientific interest has recently been aroused with reference to the origin and importance of glycuronic acid or its conjugate salts in carbohydrate metabolism, and especially in diabetes mellitus. Paul Mayer, in a series of papers, advanced the view that since glycuronic acid represents the first step in the progressive oxidation of dextrose into CO_2 and H_2O, this compound would necessarily appear as an incompletely oxidized product of dextrose combustion when, as in the incipient stages of diabetes, the body was beginning to lose its power to oxidize the carbohydrates. In substantiation of this Mayer[1] presented the results of the study of some cases of so-called incipient diabetes and of dyspnea in which he detected the elimination of glycuronates in quantities far in excess of the normal. So far as I am aware, no further notice of this point has been taken clinically, although, theoretically considered, the presence of this compound in the urine would be an invaluable aid in indicating early stages of diabetes.

This short communication deals with the search for glycuronates in the urine of patients exhibiting glycosuria of diabetic or other origin and of those who had undergone operations in which ether or chloroform had been employed. It is well known that under conditions of anesthesia the organism finds itself in a state of diminished oxidation and also that at such times, more especially after the use of chloroform, the

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* From the Department of Physiological Chemistry, Bender Laboratory. This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association. The earlier part of the work was done in collaboration with Dr. H. E. Robertson, formerly an assistant in the Bender Laboratory, who made a preliminary report at the Boston meeting (1906) of the American Medical Association. Published also in *Jour. Am. Med. Assoc.*, 1908, L, 252.

[1] Mayer (Paul); Unvollkommene Zucker oxydation im Organismus, *Deutsche Med. Wochschr.*, 1901, No. 16, 243; ibid., 1901, No. 17, 243; ibid. 1901, No. 17, p. 262.

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urine voided after operation not infrequently shows a positive (?) reaction to Fehling's test. With these points in mind, it seemed advisable to conduct a second series of tests on urine eliminated under these various conditions and to attempt to decide to what could be attributed the reducing power noticed.

Methods.—In the first series of tests the glycosuric urines were examined quantitatively as follows: By means of Fehling's and Gerrard's titration methods, by Lohnstein's newest model of saccharometer and by polarization before and after fermentation.

In the second series of determinations qualitative examination was made before and after yeast fermentation, using Fehling's, Nylander's, phenylhydrazin, orcin and polarization tests. In this way it was expected that the appearance of any substance other than dextrose could be detected. In connection with the postoperative urines a portion voided within twenty-four hours preceding the operation was examined as a control in the same manner as the postoperative sample. The anesthetics were given in the usual way, with the exception that when chloroform was employed oxygen was administered in a more or less uniform ratio to the anesthetic, this ratio depending on the character of the operation. On the average the administration amounted to fifteen minims of chloroform and three to four liters of oxygen per minute.

Before the results are discussed it becomes essential to call attention to some points as regards the manner in which the various tests were performed. No qualitative copper test for dextrose in the urine is so widely employed as Fehling's, while, at the same time, none is so carelessly performed. As a result, ambiguous findings are constantly obtained and errors in diagnosis frequently occur. The main purpose in view, when the test is applied to the urine, is to detect the presence of dextrose as against other reducing bodies, i. e., uric acid, creatinin, pentoses, lactose, etc. Since grape sugar is capable of reducing copper much more readily than any of the other compounds which might simulate it, the most suitable conditions for the test are as follows: First, the copper should exists in its most active or ionized condition; second, the quantity of the other reducing substances in the urine must become reduced to such a minimum that they are powerless to

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transform the copper while the amounts of dextrose still present remain active; third, the mixture should never be boiled after the addition of the urine. The first two conditions are met when the Fehling's solution is diluted and the urine added in much smaller quantities than is usually suggested in the various text-books on urinary analysis. The third is easily accomplished, although sufficient importance is not usually attached to it.

The disadvantages of using large amounts of urine (an equal or even one-half volume of the Fehling solution) are two-fold. In the first place, the strongly alkaline copper solution, especially in urines of high specific gravity, throws down a more or less voluminous precipitate of cupric phosphate which takes out the blue color of the solution and changes it to a dirty dark green. In the second place, the alkaline solution, acting on the ammonium salts of the urine, liberates sufficient ammonia to hold in solution small amounts of the red sub-oxid, obviously interfering with the detection of traces of dextrose. Reductions obtained under such circumstances are never typical. Very frequently under these conditions, and particularly if the mixture has been boiled even for only a few seconds after the addition of the urine, the greenish solution slowly takes on a dark, yellowish brown color, then becomes more turbid, and eventually, on standing, there separates out a finely divided, opalescent, yellowish green, cloud-like precipitate, which only settles out completely after the tube has been allowed to stand over night. In certain cases this reaction does not begin until a few minutes have elapsed after the addition of the urine. Such a reaction may be termed a pseudo-reaction. We recently had occasion to observe such changes occurring in concentrated urines of dogs even after the addition of only eight to ten drops of urine.[2] It is our conviction that this reaction is not due to the presence of an excessively large quantity of any weak reducing compound, such as may occur in the urine, but rather to the presence of one or more various conditions, a few of which are outlined above. The partial reduction of the copper occurs from causes other than the presence of dextrose, since, in the great majority of such cases, when the following details are observed, this obscure reaction never takes place.

The method of testing urines qualitatively for dextrose, as I employ and recommend it, as reducing to the lowest minimum the possibility of the above errors in results, and as efficient in easily detecting dextrose in amounts as low as 5/100 per cent., as well as in eliminating the reducing action of other compounds, is as follows: The sample is first tested

[2] Pearce, R. M., and Jackson, H. C., The Production of Cytotoxic Sera by the Injection of Nucleoproteids, *Jour. of Infect. Dis.*, 1906, III, 742

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carefully for coagulable proteids; if these are found to be present they are removed by heat and acetic acid. About four to five cubic centimeters freshly prepared, three times diluted Fehling's solution is brought just to the boiling point and immediately two drops of the proteid-free urine are added and the tube shaken thoroughly. If the urine contains over two per cent. of sugar a yellowish-red precipitate immediately appears, changing gradually to a brownish red or bright red and which settles out slowly, leaving a greenish-blue supernatant fluid. Under these conditions it is better to roughly dilute the urine with two to four volumes of water, according to the strength of the reaction, and to perform the test again.

With strengths of dextrose of from one-half to two per cent., two drops of urine tested as above will cause a characteristic precipitation of red sub-oxid of copper about which there can be no doubt. With the smaller percentages the change may come slowly, but even then heat need not be applied after the urine is added. The blue color of the unchanged Fehling's solution takes on a greenish hue and a turbidity appears which makes the mixture look somewhat smoky. This is caused by a very finely divided yellowish or red precipitate appearing in the blue solution. Little change may be seen by transmitted light, but by reflected light a brownish-red tint is evident, which finally develops into a decided light red precipitate, gradually settling out and leaving a clear blue supernatant fluid. Such a change is, of course, the typical Fehling's reaction, and when the test is performed with such diluted urine as above indicated the reaction can only be ascribed to dextrose. The pentoses, lactose and even maltose, by this method, do not give this characteristic reduction. Urines showing this reaction always give a reaction with Nylander's solution.

If no change occurs in the Fehling's solution after the addition of two drops, as above, the mixture may again be warmed just to the boiling point, and from two to four more drops added and the mixture observed. This should be repeated until in all twenty drops have been added. If nothing occurs at this point the urine does not contain dextrose to the extent of five-tenths per cent. As a routine, one then adds about one-half as much Fehling's as there is urine, boiling for ten seconds in order to obtain, if possible, the psuedo-reaction

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described above. This occurred in five per cent. of the normal urines tested by us. The time at which it appears on standing, and the depth of the turbidity and yellowish-green opalescence varies in a manner the cause or reason for which we are as yet unable to explain absolutely.

Considerable success has also been obtained in the use of Gerrard's[3] solution as a possible substitute for Fehling's quantitative procedure; while, perhaps, a little more cumbersome in its preparation than Fehling's solution, the sharpness of the end point in the titration is so greatly increased that it can be employed in some urines where Fehling's solution is impossible. Since the solution has found so little recognition in the American text-books, I detail its preparation and use.

Dilute 100 cubic centimeters of Fehling's solution with about 300 cubic centimeters of water; boil this mixture, at the same time adding cautiously an approximately five per cent. solution of potassium cyanid until the blue color has just disappeared. Then dilute the mixture to 500 cubic centimeters with water and keep in a stoppered bottle in the dark. For the titration take fifty cubic centimeters of this solution and add ten cubic centimeters of Fehling's solution. Boil the solution in a porcelain dish and run in from a burette the urine diluted so that the dextrose strength is approximately one-half to one per cent. The complete reduction of the urine is evidenced by the complete decolorization of the blue mixture. The end point is the same as in Pavy's procedure, without the disadvantageous presence of ammonia. As the double copper cyanid undergoes no reduction, the calculation takes place in the same manner as in Fehling's method, in which ten cubic centimeters are also employed. This method has been controlled with Fehling's procedure and the two give identical results. Gerrard's method is, however, the easiest to perform.

Newmann's[4] orcin test, serving to distinguish the pentoses, glycuronates and dextrose, has been extensively employed and with considerable success. Three cubic centimeters of the urine are treated with ten drops of a five per cent. alcoholic

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[3] Gerrard, (A. W.): Cyankupferreagens z. Bestimmung d. Glucose, *Jour. de Pharm. et de Chem.*, 1896, 3, 250. *Chem. Centrbl.*, 1896, 2, 135.

[4] Newmann, (A)., Neue Farbenreaktion der Zucker, *Berl. klin. Wochschr.*, 1904, No. 41, 1073.

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orcin solution and ten cubic centimeters of glacial acetic acid. The mixture is then brought to the boiling point and, after cooling, concentrated sulphuric acid is added, drop by drop, with shaking, until about twenty drops have been added. In the presence of pentoses the color becomes olive green, glycuronates turn the color violet and dextrose gives a carmine.

The other tests mentioned above were performed in the usual manner.

RESULTS.

In the first series of examinations 384 samples of supposedly normal urine of patients in the hospitals of Albany were examined in the hope of finding the pseudo-reaction mentioned above and of connecting it with the presence of glycuronic acid or glycuronates. In no case could there be determined the presence of these latter compounds in amounts more than the normal or sufficient to render it of value for diagnostic purposes.

Fourteen various samples of glycosuric urines were quantitatively examined, with the following results: Gerrard's and Fehling's quantitative methods agreed to within one-tenth per cent. The results by the saccharometer were uniformly lower and usually by one-tenth to seven-tenths per cent. This difference agreed, however, with surprising accuracy with that found in the polarization determination before and after fermentation. The figures obtained by subtracting the results of polarization before and after fermentation correspond to saccharometer readings to within one-tenth per cent.

These facts indicate that both quantitative copper tests include substances which are not dextrose and which turn the plane of polarized light to the left to the extent of from one-tenth to seven-tenths per cent. (calculated as dextrose). The saccharometer readings do not include these compounds, hence they are not fermentable. As a conclusion from these examinations we may say that in these urines glycuronic acid or its salts was not present in excessive amounts.

In the second series of examinations attention was turned to the postoperative specimens in the hope that in the condition of diminished oxidation following anesthesia glycuronates

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might be detected in abnormal amounts. All the samples were voided within twelve hours after operation. In all 273 specimens were examined, of which 261 were voided after ether anesthesia, eleven following chloroform and one after a mixture of the two. Examination of the urines previous to the operations showed no reducing compounds to be present. Subsequent to the operations eleven samples of urine, voided after ether, gave positive reductions with Fehling's test, and on further investigation the reducing substance was shown to be dextrose in amounts from two-tenths to one and three-tenths per cent. The length and character of the operation apparently has no effect on the amount of dextrose eliminated. The patients were persons from twenty to thirty-five years of age. None of the chloroform samples or the chloroform-ether sample resulted positively. This is probably to be explained by the use of oxygen during the operation, thereby preventing diminished oxidation in the tissues.

CONCLUSIONS.

1. Dextrose appeared in four per cent. of 261 samples of urine collected after operations in which ether was employed.

2. Neither glycuronic acid nor its conjugate salts are eliminated in the urine under conditions of diminished oxidation, such as occur during diabetes mellitus and ether or chloroform anesthesia, when the latter is combined with oxygen.

3. The pseudo-reduction obtained in about five per cent. of normal urines is to be ascribed to faulty methods of performing the test. It is not due to an increase in amount of uric acid or creatinin.

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A CLINICAL STUDY OF HYPERNEPHROMA, WITH PATHOLOGICAL REPORTS.*

By GEORGE E. BEILBY, M. D.

Assistant Attending Surgeon, Albany Hospital.

Since the recognition by Grawitz (1), in 1883, of the adrenal origin of a certain class of tumors arising in the kidney, there has appeared an abundance of literature bearing upon the subject. Grawitz's views were, at first, vigorously opposed by Sudeck (2), Driessen (3), Hansemann (4), Hildebrand (5), and other writers of note, who maintained that these tumors were of endothelial origin and denied the possibility of their relation to the adrenal body or aberrant adrenal tissue. Later studies, however, entirely confirmed the views of Grawitz; so that, at present, we have a well-recognized type of tumor arising from adrenal tissue, which may spring from a normally placed adrenal body, or from aberrant adrenal tissue. The term "hypernephroma," as a designation of this class of tumors, was first employed by Birch-Hirschfeld (6), in 1896, who recognized "typical and atypical, or benign and malignant hypernephromas, and, according to their origin, cortical and medullary forms." This term has come to include tumors of this character occurring not only in the kidney, but arising from adrenal rests outside of the kidney tissue; so that, at present, while it may be said that the histogenesis of these growths is thoroughly established and their pathological anatomy fairly well determined, they are among the most difficult of recognition and their clinical course and symptoms are not well defined.

The importance of early recognizing these tumors is apparent. As a rule, in the early stages they are of a benign nature, and their growth slow; and it may be months, or even years, before they metastasize, or present other signs of malignancy.

It is, therefore, mainly with the hope of adding something to the meager clinical data which we possess in regard to this condition, rather than with the idea of adding to our pathological knowledge, that this series of cases is presented.

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* Published also in *Surgery, Gynecology and Obstetrics*, 1908, (Sept.), ii, 279.

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CLASSIFICATION OF CASES.

Under the general term of hypernephroma are included all tumors arising from adrenal tissue, whether this be at the normal site of the adrenal gland, from adrenal "rests" within the kidney substance, or at remote localities throughout the body. Further classification upon a purely histological basis has been attempted by some pathologists. Thus, Ohlmacher (7) designates a cortical and a medullary hypernephroma, depending upon whether the new growth reproduces the cortex or the medulla of the adrenal. This author reports a case of "malignant medullary hypernephroma." I have been unable to find other cases of this character in the literature, and the cases reported in this series have the histological appearance of the cortical rather than the medullary portion of the adrenal, with one possible exception. It is probable that the medullary form of growth is extremely rare, but future observations may enable us to develop a classification upon a histologic basis.

It seems that we might properly designate, at least clinically, a benign and a malignant form, for it is well known that many of these new growths may exist for years without presenting evidences of malignancy, while others rapidly invade the surrounding tissues and metastasize early; the latter group, however, may represent but a second stage of the former.

Material. The material forming the basis of this report comprises eleven tumors removed surgically, and examined at the Bender Laboratory during the past twelve years, and four autopsy specimens, which have accumulated during a like period of time. In two of the four post-mortem cases the hypernephroma, which was small, occupied the normal site of the adrenal body. Their presence was not suspected during life, the patients having died of some other disease. In the other two autopsy cases the hypernephroma arose within the kidney, in one of which were revealed two definite types of growth—sarcoma and hypernephroma, with metastases of the former growth to the liver. An attempt has been made to obtain, as far as possible, complete clinical histories of the surgical cases and the ultimate results in each instance.

These tumors may be divided as follows:

1. Hypernephroma (or adenoma) of the adrenal body (non-

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malignant), two cases; in one instance the growth was bilateral.

2. Hypernephroma of the kidney (hypernephroma renis), nine cases.

The two cases of adrenal hypernephroma (adenomata) were discovered at autopsy. In one case (Bender Laboratory Records, autopsy No. 0-848), that of a woman aged sixty, death was due to chronic diffuse nephritis and thrombosis of the superior longitudinal sinus. The right adrenal measured 4 x 4.5 x 1.5 cm., and within its medullary portion was an oval yellowish mass, measuring 1 x 2 x 2 cm., surrounded by well-defined adrenal cortex. The mass was apparently a small adrenal tumor. Its cut surface was greyish-yellow in color. Microscopical examination showed the tumor to be composed of adrenal tissue.

The other case was one of dementia paralytica (Bender Laboratory Records, autopsy No. 0-497). Male, age not stated.

Anatomical diagnosis. Arteriosclerosis of aorta, iliac, and coronary arteries. Brown atrophy of heart, with slight interstitial myocarditis (papillary muscles). Senile emphysema of lungs with healed tuberculous foci and acute bronchopneumonia. Slight chronic passive congestion of liver. Bilateral hypernephromata (adenomata) of adrenals. Here both adrenals showed the presence of new growths, the one in the left small, but in the right the growth forms a distinct nodule eight millimeters in diameter, which is composed of yellow, cortical substance.

In neither of these cases do the records show that the adrenal growth presented any symptoms during life which could be attributed to their presence. They are reported in this connection only to complete our series.

Hypernephroma renis. Nine cases. Surgical seven, autopsy two. During twelve years, in which time 1,200 autopsies have been performed at the Bender Laboratory, we have encountered but two instances of hypernephroma having its origin within the kidney. While I have been unable to obtain any clinical data of these cases, the pathological reports seem of sufficient interest to warrant recording.

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CASE I. Autopsy by Dr. Blumer (Autopsy Records, autopsy No. 11). Only a partial autopsy was made about thirty-six hours after death. Aged male.

Adrenals. Normal.

Right kidney. Capsule strips off with some difficulty, tearing away small pieces of kidney substance. The surface shows well-marked fetal lobulations. It is finely granular and somewhat congested. At one point, a cyst the size of a walnut, and containing a clear fluid, projects from it. On section, the cortex is considerably diminished. Cortex markings indistinct. Glomeruli visible and pale. Medulla congested, but otherwise normal. Pelvis normal.

Left kidney. The position of the left kidney is occupied by a mass the size of two fists. It has, in general, a kidney shape. Its surface is coarsely lobulated, and is adherent to the surrounding structure by firm adhesions. Its consistence is moderately firm. On section, it presents a mottled appearance. Its main bulk is made up of a greyish-white, translucent, homogeneous structure. Here and there, are areas of this structure which have taken on a greenish color, presumably the result of degeneration. This appearance varies from greenish to a dry, chrome yellow, the tissue in the latter event resembling very strikingly the appearance of the cortical adrenal substance. The adrenal gland on the same side is attached to the tumor mass, but apparently not invaded by tumor substance. At one point is an area, some three centimeters in each direction, lined by smooth, mucous membrane. This lies in the part of the tumor which corresponds to the hilum of the kidney, and is presumably the remains of the pelvis. Considerable portion of medulla of kidney remains unchanged, growth springing from cortex.

Aorta shows extensive atheromatous changes, with marked calcification.

Liver. The organ has a peculiar shape. Right lobe is much elongated in downward direction. Left lobe is very small. Surface is free from adhesions, a brownish-red color. Scattered over the surface are a number of yellowish, slightly elevated nodules, varying in size from a pea to a marble. On section, the organ is somewhat cloudy. Nodules seen on the surface are found to extend into the substance of the organ. The depth of their extension generally corresponds to their surface diameter. Scattered through the substance of the organ in its depths are a number of similar nodules. On section, they have a homogeneous, whitish-yellow, translucent appearance. The walls of the gall-bladder are thickened. It contains small amount of thick, mucus-like material and three or four dark, facetted gall-stones the size of marbles.

Anatomical diagnosis. Primary sarcoma of left kidney. Metastases to liver and retroperitoneal glands. Chronic diffuse nephritis with cyst formation. Cholelithiasis. Hypertrophy of the prostate. Contracted bladder. Atheroma of aorta.

THE TUMOR.

The tumor presents, in different parts of its substance, two entirely different structures. In places one type predominates over a large area; in places the other type predominates over a large area; while, in still

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other places, the two adjoin each other, the one apparently invading the other, as will be described below. The one type of tumor presents the following appearances: Under the low power, it is apparently made up of a series of fairly regular spaces, having thin walls, and containing a few scattered nuclei. Under the high power, it is seen that the walls of these spaces are made up of fine bands of connective tissue. The spaces are lined, in some places, by flat cells similar to those lining those of normal blood or lymph vessels. The scattered nuclei, which were seen with the lower power in the spaces, can now be made out to belong to large, exceedingly pale cells, which fill the spaces, and which are apparently proliferated endothelial cells. At no place in the section, which is an alcohol-hardened one, can red blood corpuscles be seen, notwithstanding the fact that their shadows can easily be made out in the adjacent vessels. At one or two places in the tumor spaces are objects which suggest shadows, and, in an occasional space, the polynuclear leucocytes may be seen. There are distinct blood-vessels running through the tumor, but no connection can be made out between them and the spaces. Although the tumor presents all the appearances of an angiosarcoma, it seems probable that it sprung from the lymph and not the blood vessels.

The other type of tumor, present in the growth, is made up of cells without any definite arrangement, between which run irregular bands of connective tissue. The cells in this growth vary considerably in size and appearance. Taken as a whole, they are large cells. Their shape varies, some being round, some oval, and many of them quite irregular. The amount of protoplasm varies, some showing but a narrow rim, while in others the amount is great. The nuclei have a peculiar refractive look, and the chromatic network is very sharply marked. Scattered throughout the tumor are quite a number of multi-nucleated cells, many of which are large enough to deserve the name giant cell, and some of which have distinct budding nuclei, such as are seen in certain cells of the bone marrow. Where the two types of tumors meet, one gets the impression that the angiosarcoma is being invaded by the other growth, and the invasion is apparently taking place by the progression of the latter along the connective tissue of the former.

Liver. Outside of the metastasis to be described later, the liver shows areas of localized dilatation of the blood-vessels (probably from pressure of tumor nodules), a swollen and granular condition of the liver cells, and occasional fat spaces. The tumor metastasis, which causes a certain amount of compression of the surrounding liver substance, resembles the second type of growth described. The cells, however, do not differ nearly so much in size as they did in the original growth, nor are there present any such number of the large multinuclear cells, or of the cells with budding nuclei. In fact, both of these latter are almost absent.

Kidney, for some reason, stains very poorly. Capsule absent. Occasional areas or new-formed connective tissue in center and few similar areas in kidney substance. Most of the glomeruli normal. Here and there, an atrophied one is seen. Kidney cells swollen and granular. Blood-

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vessels show well-marked obliterative endarteritis. Occasional hyaline cast is seen in tubules.

CASE 2. Autopsy by Dr. Pearce (Autopsy Records, No. 1147). Male, sixty years of age.

Abdomen. A small amount, about 300 cubic centimeters, of clear, straw-colored fluid is found in the pelvis. Appendix normal. Mesenteric lymph-nodes normal. In the left flank is found a large, lobulated mass, corresponding to the position of the kidney, and adherent to the adjacent structures.

Right kidney. Smaller than normal. Capsule peels readily, leaving a coarsely granular surface, with here and there a few small cysts. Cortex is greatly diminished, being less than one-half the normal amount, and is firm and greyish-red in color. Pyramids are injected. In the pelvis is an increased amount of fat. On the surface of the kidney, and projecting from it as a globular mass, is a tumor two centimeters in diameter, of soft consistence, uniformly yellowish in appearance, and distinctly encapsulated.

Left kidney is similar in appearance to right, but adherent to and involving its upper pole, is a bilobed mass, twice the size of the kidney itself, which is soft and fluctuant and suggests the presence of cysts. On section, however, these masses are found to consist of a new growth, which has become completely necrotic and which presents in part a uniform, rather firm, yellowish, necrotic tissue, and, in part, soft, red, grumous material mixed with old blood. The position of the tumor, which is distinctly encapsulated and separated from the kidney substance, although it impinges upon the kidney, presents here and there small portions of tissue which have not undergone necrosis and which indicate it to be of adrenal origin. Moreover, the adrenal on this side cannot be found.

Anatomical diagnosis. Arteriosclerosis. Chronic diffuse nephritis (interstitial type). Fatty transformation of the myocardium. Large necrotic hypernephroma involving left kidney. Small hypernephroma of right kidney. Subacute esophagitis. Chronic congestion of liver. Emphysema of lungs. Moderate hydroperitoneum and hydrothorax. Malformation of sternum (old fracture?).

Microscopic diagnosis. Chronic interstitial nephritis with hyaline degeneration. Subacute esophagitis. Papillary adenoma of kidney. Necrotic hypernephroma.

SURGICAL CASES.

CASE 1. Male, aged fifty-eight, was admitted to my service in the Albany Hospital, October 10, 1907. His family history was unimportant. He states that he has always been in good health till the onset of the present trouble, which began seven years ago. At this time, while picking fruit in a tree in a strained position, he felt something "give way" in his right side. The sensation was so noticeable that it was mentioned to his wife.

Two days later, blood appeared in the urine, and persisted for two or three days, but was not accompanied by pain. The patient experienced no

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trouble for a year and a half, during which time he felt perfectly well, when there appeared a second attack of hematuria of greater severity than the first and its onset was accompanied with colicky pain and chills, the pain radiating from the back to the perineal region and penis. The flow of blood was so profuse that clots obstructed the urethra and catheterization was necessary. This attack continued for about a week, when there was complete cessation. From this time until about six months ago (four and one-half years), the attacks of hematuria recurred at intervals of four or six months, each time lasting from two days to a week. During the last six months they have occurred more frequently. From frequent catheterizations the patient has developed a severe cystitis. During the last year he has lost about ten pounds in weight.

Physical examination. The patient is a strong, muscular man, well nourished, with a slightly sallow complexion. The superficial arteries show no signs of sclerosis. Pulse eighty, strong and regular. Examination of the heart and lungs gives no evidence of disease of these organs. There is a decided fullness in the right flank below the costal margin where, on palpitation, a tumor, measuring approximately ten by eighteen centimeters, can be made out. It occupies the lumbar region and extends forward to the nipple line. It moves slightly with respiration. It presents a smooth, anterior surface, and suggests in its shape and position a tumor involving the kidney. A skiagraph was made and at about the center of the tumor mass a small shadow, about the size of a pea, was seen, which was interpreted as revealing a small kidney stone. In view of the history and X-ray findings, a clinical diagnosis of cystic kidney was made.

Urine examination. Sp. gr. 1018, acid, no sugar, trace of albumen, pus and epithelium abundant.

Operation, October 12. Chloroform and oxygen. Lumbar incision. Kidney was found adherent to the surrounding fat, from which it was separated with considerable difficulty. On account of its size, the mass could not be delivered until the incision was extended well forward along the ilium. The pedicle of the kidney was clamped and the organ removed. On account of the extensive involvement of the vessels by the new growth, their ligation was impossible. Clamps were left in situ. Several large gauze wicks were carried down to the stump of the renal pedicle, and the external wound partially closed with interrupted silkworm gut sutures. Salt solution 1,000 cubic centimeters were given subcutaneously. There was considerable operative shock, but the patient responded well to treatment, and his condition after twelve hours was good. During the first twenty-four hours following the operation, only three and one-half ounces of urine were obtained per catheter. By the employment of diuretics and the introduction of large amounts of saline solution, the daily output of urine was gradually increased, so that on the sixth day after the operation thirty-eight ounces were obtained, which had a fair specific gravity, but contained a large amount of albumen. The patient early developed symptoms of uremia and died on the seventh day after operation.

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Pathological report (Bender Laboratory Records, Surg. Path., No. 07-1348. See Fig. 1).

Gross description. Specimen consists of a kidney, measuring 14 x 8.5 x 7.5 centimeters. Outer surface is very irregular, in places of a nodular character. It is throughout the greater part mottled greyish-red in color, nodules being bright yellow. At hilum these nodules are more marked, and a mass measuring four centimeters in diameter, apparently having its origin in the pelvis, is present beneath the capsule. These nodules vary in size, from pin point to the above mentioned. Some are solitary, while others are conglomerate. On section, the pelvis is considerably dilated and distorted and, in part, the calices are obliterated. Cut surface of the kidney substance shows it to be pale greyish-brown in color, and anatomical markings are obliterated. Distributed throughout are numerous, slightly elevated, yellow areas of various shapes and sizes. These nodules are somewhat firm, but one has broken down and presents slight hemorrhage. About some of these nodules the tissue is dark brown, due to old hemorrhage.

Anatomical diagnosis. Multiple hypernephromata of kidney.

Microscopic description. Sections of kidney. The entire cortex and medullary portions are extensively replaced by connective tissue, the greater portion being composed of young cells. Many tubules are compressed and obliterated, some containing hyaline casts and denuded of epithelium. Others are dilated. Many glomeruli are partly or entirely replaced by fibrous connective tissue and the capsules greatly thickened. In the section are areas of cuboidal cells which stain poorly and contain fat globules. These nuclei are found and show no definite arrangement. About them the connective tissue is fibrous and contains considerable free blood and pigment.

Microscopic diagnosis. Hypernephromata of kidney.

Autopsy by Dr. Hacker (Bender Laboratory Records, autopsy No. 1188).

Anatomical diagnosis. Absence of right kidney (due to operation). Incised wound of right side, with necrosis (due to operation). Hypernephroma of perinephritic fat (right side), with invasion of inferior vena cava. Chronic interstitial nephritis. Cholelithiasis. Hydroperitoneum. Hydrothorax. Hypostatic congestion of left lung. Emphysema of lung. Anthracosis of lung.

Kidneys. The left kidney is enlarged and measures 11 x 6.3 x 5 centimeters. The capsule, in places, is adherent. The surface is pale and presents numerous points of retraction. Beneath it are occasional cysts, the largest one centimeter in diameter. The cut surface is pale and opaque. The cortex is thickened and markings are indistinct. Numerous cysts are present, and at the lower pole in one pyramid is a circumscribed, soft, brownish-yellow nodule one and two-tenths centimeter. The right kidney is absent. In the right renal region the tissue is infiltrated by blood and necrotic material. Behind the right renal vein is a soft, friable mass, measuring approximately 5 x 3 x 2 centimeters. The portion bordering on the wound is soft, pinkish-brown, but anteriorly it is soft and bright yellow. The latter penetrates the posterior wall

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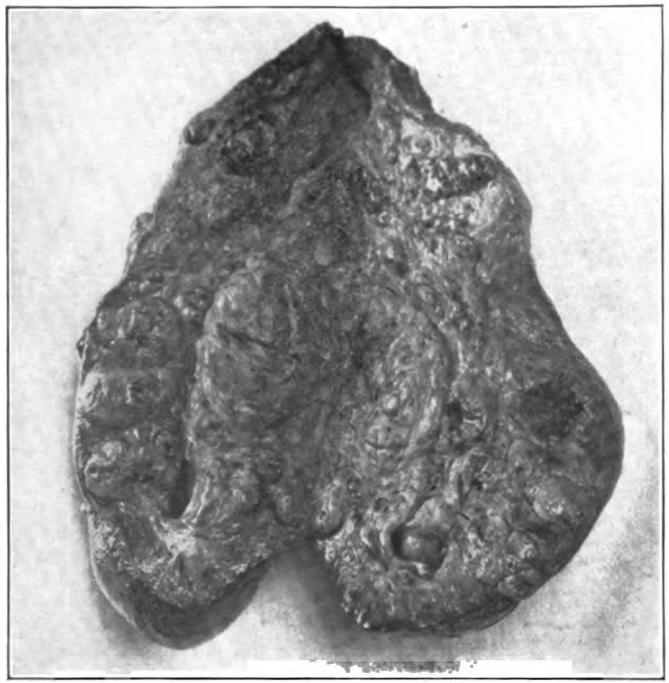

FIG. I. Photograph of Multiple Hypernephromata of **Kidney.** ⅓ actual size. Surgical Case I.

FIG. II. **Photograph Showing Hypernephroma Invading** Vena Cava. ⅓ actual size. Case I.

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of the inferior vena cava and forms a pedunculated mass, which fills the lumen and extends into both renal veins (See Fig. 2). This mass is soft, bright yellow, and freely movable about the pedicle. It measures approximately 4 x 3 x 1.8 centimeters. About four centimeters from the inferior vena cava, the right renal vein presents a small, bluish-brown, eroded area.

Microscopic description. Right kidney. Throughout there is an irregular increase of connective tissue and beneath the capsule are areas composed chiefly of small, round cells. In the cortex, many of the tubules are lined by swollen and granular cells, which entirely fill their lumina. Toward the pelvis, many are contracted and filled with hyaline material. Others are dilated. The lumina of many tubules are filled with desquamated epithelium. Many cells contain fat globules. Many glomeruli show proliferation of young connective tissue, some of which are entirely transformed into fibrous tissue with hyaline degeneration. The veins are engorged and dilated. The arteries show thickening, chiefly the intima, while many capillaries show obliteration with hyaline transformation. At one point is an area composed of processes of fibrous tissue covered by cuboidal cells, many of which have a brown granular material. In places these processes have undergone necrosis. Within the necrotic material are numerous blood corpuscles, pigment, and cholesterin spaces. About this area is a dense, fibrous capsule in which are a few spaces lined by a single layer of cuboidal cells. The nuclei of these cells are round and stain deeply. In the region of this area are several cysts containing a mucoid substance. These cysts are lined by a single layer of low cuboidal cells. Throughout many sections are occasional small areas filled with densely packed, irregularly arranged cells, which resemble in structure those in the area above described. The arteries show marked thickening of the intima and the capillaries show increase of connective tissue, with hyaline transformation and obliteration.

Left adrenal. Irregular areas are composed of cells showing marked infiltration of glycogen. The capillaries show marked thickening with hyaline transformation. Many are obliterated.

Right adrenal. Similar to left.

Retroperitoneal mass at base of wound. The greater part is composed of large cells having a tubular arrangement and in which are globules of glycogen. The greater part of the tissue is necrotic and the capillaries are distended with colonies of bacteria. In part, the necrotic material is markedly infiltrated by polynuclear leucocytes. The remaining tissue is edematous and contains many leucocytes.

Microscopic diagnosis. Hypernephroma of lumbar region, with necrosis and suppuration. Hypernephromata of right kidney. Chronic interstitial nephritis. Chronic myocarditis. Chronic passive congestion of lung, liver, and spleen. Arteriosclerosis. Chronic cystitis. Slight chronic pancreatitis. Acute bronchopneumonia. Anthracosis, emphysema, and atelectasis of lung. Encapsulated papillary adenoma of right kidney.

CASE 2. Service of Dr. MacDonald. Mr. T. S., aged forty-six years. Duration of disease six months, following a fall in which he was struck in the region of the right kidney. Symptoms of onset, pain, originating

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in right lumbar region and referred downward to penis, hematuria accompanying pain. Recurrent attacks for six months.

Clinical diagnosis. Stone in kidney.

Operation. Removal of right kidney.

In February, 1908 (five and one-half years after operation), patient was in good health.

Pathological report (Bender Laboratory Records, Surg. Path. No. 97-14), September 4, 1902.

Gross description. Specimen consists of a kidney measuring 5 x 2 x 1.5 inches. The fatty and fibrous capsules have both been removed, leaving a smooth, mottled surface. The prevailing color of the surface is yellowish-brown, the mottling being due to numerous pin-head areas of hemorrhage. The upper pole of the kidney is enlarged, and there are present on the surface of the enlarged portion a number of yellowish tumor nodules, covering from one-sixteenth to three-eighths of an inch in diameter. These nodules are rounded, soft in consistence, and smooth, and are of yellowish color. On section of the kidney, the main portion of the organ is relatively normal. The cortex is slightly swollen and quite pale. Glomeruli congested. The pelvis shows a number of discrete and confluent hemorrhages. The tumor nodule measures an inch and five-eighths in diameter. It is roughly globular and occupies one pole of the kidney and projects into the pelvis. One point of the tumor is soft, and in places distinctly hemorrhagic, and is made up of a yellowish cellular growth, which has the appearance of adrenal tissue.

Anatomical diagnosis. Hypernephroma of the kidney.

CASE 3. Service of Dr. Vander Veer. Mr. G. W., aged thirty-five. Complains of tumor in the left abdominal region. Onset five years ago, with pain in the region of the tumor. Attack lasted three days. Ten days ago, first noticed a bunch in left side of abdomen, which has increased some in size since then. Patient has lost in weight and feels perfectly well. Urinary examination showed granular, hyaline, and epithelial casts, some mucus, some epithelia, clear amber, sp. gr. 1020, no sugar, trace of albumen.

Clinical diagnosis. Sarcoma of kidney.

Operation, May, 1905. Removal of left kidney. In November, 1907 (two and one-half years since operation), patient was well. Had gained fifteen pounds in weight. Urine was normal. No evidence of metastatic or recurrent growths.

Pathological report (Bender Laboratory Records, Surg. Path., No. 05-537).

Gross description. Specimen consists of a kidney, from the cortex of which projects a definitely encapsulated cystic tumor, measuring from twelve to sixteen centimeters in diameter, and having a base measuring 10 x 3 centimeters. The center of this base corresponds to a point situated on the surface of the kidney, opposite the hilus and at a point corresponding to the junction of the upper and middle thirds. On section, the tumor is found to have a firm, fibrous capsule, averaging from three to five millimeters in thickness, and a softened center, consisting of a grumous, blood-stained, necrotic-looking material, with coarse

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tags of fibrous tissue extending in from the wall of the cyst. The cyst extends into the kidney as far as the pelvis and the kidney cortex is reflected over the surface of the tumor, for a distance of four to five centimeters, at the base. The remainder of the kidney shows nothing noteworthy. The general picture is that of a tumor, originally composed of large, cellular areas and coarse interstitial fibrous bands, which has undergone extensive necrosis.

Anatomical diagnosis. Hypernephroma with extensive necrosis and softening.

Microscopic description. Sections show capsule composed of dense fibrous tissue with areas of calcification and true bone formation. The contents of the cyst are, for the most part, almost completely necrotic, but immediately adjacent to the capsule, and partly infiltrating it, can be be seen irregular islands of large, polyhedral, vacuolated cells having the general characteristics of adrenal cells. These cells are arranged in irregular masses, and, in some areas, have an indefinite, glandular arrangement. In other sections, new-formed blood-vessels can be seen extending from the capsule into the necrotic, hemorrhagic cysts contents.

Microscopic diagnosis. Adrenal tumor with extensive central necrosis and softening and hemorrhage, together with calcification and bone formation in capsule.

CASE 4. Service of Dr. Madill, of Ogdensburgh, N. Y. Mrs. K., aged thirty-three. Duration of disease about five months. Symptoms anemia, loss in weight, and pain of a dragging character in the region of the left kidney. No urinary symptoms (patient had suffered from neurasthenia for over a year, and the tumor of the kidney was discovered while making an examination).

Clinical diagnosis. Tumor of kidney.

Operation. Nephrectomy, left.

Recovered from operation rapidly and improved for about four months. Then again became anemic, lost weight, and died ten months after operation (definite cause of death not known. No evidence of recurrence or metastases).

Pathological report (Bender Laboratory Records, Surg. Path. No. 06-55).

Gross description. Specimen consists of a large, distorted kidney. Capsule strips fairly readily from one pole, which measures 7 x 6 x 3 centimeters. Opposite pole is enlarged by a circular tumor mass so that it measures 10 x 7 x 5 centimeters. Entire kidney is about thirteen centimeters in length. Mass is six centimeters in diameter. Kidney substance is normal in consistence, except over mass, where softened areas are felt. Considerable amount of fat is found in pelvis. Over tumor, color is a reddish to a yellowish-white. Remainder of kidney is pale and dark reddish-white in color. Cut surface shows the tumor mass to be well encapsulated, yellowish-white in color. Several areas of hemorrhage near periphery. The remainder of tumor surface contains scattered areas of increased consistence and waxy appearance. In the remainder of the kidney, cortex and pyramids are very pale. Pelvis contains a large amount of fat. Malpighian corpuscles are seen.

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Anatomical diagnosis. Adrenal adenoma arising in kidney.

Microscopic description. Section of kidney and tumor mass shows tumor surrounded by a compact layer of kidney pulp, beneath which and in body of tumor are found areas of hemorrhage. Tumor is made up of a fine, reticular stroma, in which are large epithelioid cells with vesicular nuclei. Cells are arranged in cords and masses. Protoplasm does not stain well, is translucent and vacuolated, and contains a few granules. Many large areas of necrosis occur, accompanied by infiltration of leucocytes and lymphoid cells. Renal tissue proper shows cloudy swelling of tubular epithelium.

Microscopic diagnosis. Adrenal adenoma.

CASE 5. Service of Dr. Van Loon. Mrs. D. Z., aged fifty-two. Family history negative. Patient has had attacks of "stomach trouble" for several years. One week ago, a definite attack of biliary colic. Upon examining the abdomen at this time, a tumor of the right kidney was found. Urinary examination negative.

Clinical diagnosis. Gall-stones, tumor of right kidney.

Operation, May 11, 1907. Cholecystotomy, removal of gall-stones, nephrectomy, right kidney and tumor. Good recovery. In February, 1908 (eight months after operation), patient was well.

Pathological report (Bender Laboratory Records, Surg. Path. No. 07-670).

Gross description. Specimen consists of a pyramidal-shaped mass, measuring approximately 18 x 12 x 8 centimeters through its broadest diameters. The mass is encapsulated and the broader half is greyish-yellow and soft, while the remaining portion is firmer and greyish-brown On section, the cut surface of the soft portion is pale, brownish-yellow, and pulpy; from it there exudes a brownish-pink fluid. The remaining portion, on section, presents the cut surface of a kidney. The two portions gradually fade into each other.

Anatomical diagnosis. Hypernephroma of kidney.

Microscopic description. Sections show trabeculæ and gland-like spaces, composed of polygonal or cuboidal cells, arranged in an irregular manner. In parts necrosis is seen and extensive hemorrhage.

Microscopic diagnosis. Hypernephroma of kidney.

CASE 6. Service of Dr. Macdonald. Mr. D. J., aged forty-nine. Clinical history not obtained. Patient died twenty-four hours after operation.

Pathological report (Bender Laboratory Records, Surg. Path. No. 04-860).

Clinical diagnosis. Sarcoma of left kidney.

Gross description. Specimen consists of a much enlarged and degenerated kidney which has been bisected. Each half measures about 16 x 12 x 3 centimeters. External surface of one-half is smooth and glistening. The other surface is uneven and denuded of covering in places. On section, find but little evidence of normal kidney tissue, and that is near periphery. Surface, as a whole, presents a necrotic, honey-combed appearance. Strands of white, fibrous tissue, fairly hard to feel, radiate in all directions. These areas are intermingled with yellowish patches, some of them being necrotic and filled with cheesy-like material. In still other

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places, the surface presents a pearly-white appearance. Some evidence of hemorrhagic areas in cortex, there being a few blood clots.

Anatomical diagnosis. Hypernephroma of kidney.

Microscopic description. Large masses of cells with round, lightly staining nucleus and large amount of protoplasm, which is greatly vacuolated and resembles the structure of adrenal cells. Between these masses are large bands of more or less hyaline connective tissue. Some portions of tumor are entirely necrotic.

Microscopic diagnosis. Hypernephroma.

CASE 7. (From Ellis Hospital, Schenectady, N. Y.) I have been unable to obtain any clinical history of this case other than that which was appended to the specimen upon its receipt at the laboratory. It was said to be a left kidney which had been growing for seven years; patient suffered from intermittent hematuria.

Pathological report (Bender Laboratory Records, Surg. Path. No. 04-1054).

Gross description. Specimen consists of an oval tumor mass, measuring 24 x 17 x 14 centimeters. The surface is roughly lobulated and covered with coarse tags of fibrous tissue, the entire mass having a firm, fibrous capsule. On section, the mass is seen to consist of multiple globular, usually definitely encapsulated, tumor masses, ranging from one to four centimeters in diameter. These masses, are separated from one another by firm sheets of fibrous tissue which retract on section. The non-degenerated portions of the new growth present a light pink, distinctly granular, cut surface; others are softened and present a yellowish, fatty-like surface; while others are hemorrhagic, and a few are represented by cavities filled with a hemorrhagic fluid.

Anatomical diagnosis. Hypernephroma.

Microscopic description. Sections show stroma of connective tissue imbedded in which are large polyhedral cells, lying in irregular columns. These cells show marked vacuolation, with some pigmentation resembling adrenal cells.

Microscopic diagnosis. Adenoma of kidney with cells resembling adrenal cells (hypernephroma).

SYMPTOMATOLOGY.

The four cases reported from our autopsy records did not present, as far as can be determined, any symptoms attributable to the hypernephroma. The clinical history of one of the surgical cases was not obtainable, leaving us only six cases on which to base our clinical data. The symptoms of importance, which were fairly constant, were three in number, *pain, hematuria* and *tumor*. Pain was present in four of the six cases, in three of which it was of the type described as renal colic, and was accompanied by hematuria. Without doubt, the pain in these cases is due to the passage of blood

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clots from the pelvis of the kidney to the bladder. In the fourth case, the pain was confined principally to the region of the tumor, and radiated backward to the spinal column.

The most frequent form of pain, then, is that accompanying the hematuria, and it differs in no way from that caused by the passage of other foreign bodies along the ureters. It is usually not as severe in character as that produced by calculi. The hematuria, if slight in amount, may occur without pain. It is frequently the first symptom noticed. In all of our observations it was intermittent in character, lasting from a few hours to several days, and appearing at intervals from a few months to several years. In one case, the hemorrhage was usually very profuse, often filling the bladder with clotted blood and obstructing the urethra.

Apparently the size and location of the growth within the kidney substance had little bearing upon the occurrence of this symptom; for, in two instances where the pathological examination showed the tumor to be of large size and to involve the renal pelvis, there had been no hematuria. A tumor that is easily palpable, or that the patient discovers, is necessarily a late symptom and, if one on which we rely to make a diagnosis, often appears too late to offer our patient a good chance of recovery.

Location. In six of the ten cases of hypernephroma of the kidney, the tumor was found upon the left side.

General symptoms are usually absent in the early stages. With prolonged and severe bleeding, secondary anemia is marked, and the patient may lose considerable weight. In one case the condition was associated with neurasthenia.

Aside from the presence of blood, there were no significant urinary changes. One case had a severe cystitis, probably from catheterization, and in two there were evidences of a chronic nephritis, albumen, and urinary casts.

Age. The youngest patient was thirty-three, the oldest sixty years; average age forty-eight years. The average age of onset, as indicated by the appearance of symptoms, was forty-one years.

Sex. In one case, the sex was not stated. In six cases, it was found four times in the male and twice in the female.

Duration. It is obviously difficult to ascertain, even approximately, the length of time that many of these tumors

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have been present. In two of our cases, while the growths had attained large size, they had presented no symptoms which attracted the attention of the patient, and they were discovered by the physician upon examination. It is only in those cases, in which hematuria and pain are manifest, that we can base any accurate knowledge of the length of time which the tumor has been present. I think it may be said that, almost without exception, this type of growth is slow in progress, especially in its early stages, and attains palpable size only after several years of existence. In two cases in this group hematuria had been present for seven years. Tumors presenting symptoms for shorter periods of time, gave no indications, histologically, of being of a less malignant type.

Diagnosis. Unfortunately these tumors of adrenal origin, whether arising within the kidney substance or at the normal site of the adrenal body, present no pathognomonic symptoms. For a diagnosis we are largely dependent upon three symptoms, ***hematuria, pain*** and ***tumor,*** which are alike suggestive of other and more common kidney lesions. As far as I am aware, those growths arising outside of the kidney never present symptoms, except tumors and, perhaps, metastases, both of which are necessarily late manifestations. It may be said that rarely is a correct diagnosis of hypernephroma made previous to operation. This is unfortunate, since it is clearly demonstrated that these growths, at least the majority, are of a benign character in their early stages, and that, when thoroughly removed at this time, they show no tendency to recur. It seems that, clinically, we may recognize two groups of ***hypernephroma renis:*** Cases associated with hematuria; and cases without. Obviously, the cases without hematuria present no early symptoms whatever suggestive of renal lesion, so that in this group, ***tumor*** and, rarely, pain are the first manifestations. This was true in three of our six cases in all of which the growth had attained considerable size. In one of these cases, death occurred within a few days after operation, and in another, after a few months. In this latter case, while it was not demonstrated that death was due to metastases, this seemed to the surgeon to be the probable explanation. In the other group of cases where hematuria is present we are given a clue to the condition, and by a process of exclusion we should be able, at least, to make a tentative diagnosis of

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hypernephroma. An exploratory operation should then be done. Three of our cases had hematuria early in the disease and in each instance it was associated with "colicky" pain. In a study of the cases collected by other observers, we are led to believe that *hematuria* and *pain* are present more frequently than indicated by our series. Thus Keen and Pfahler (8) found hematuria in nineteen out of twenty-six cases. Cases, then, presenting the symptom of hematuria should always be approached with this possibility in mind, and we should exhaust every means at our command to confirm or exclude hypernephroma. A question in regard to these cases, which has never been thoroughly investigated, is that of increased arterial tension. It is logical to suppose that, with an increase of adrenal tissue, we may have an excess of adrenal secretion, which would result in a rise of blood-pressure. Certain writers have noted that this was true; but observations upon this point, sufficient to settle the question, have not yet been made. Every case of hypernephroma should be thoroughly investigated in this regard, and we may find that a study of the blood-pressure furnishes us a valuable aid in diagnosis.

Prognosis. I think it can be safely said that, in the majority of cases of hypernephroma, an early removal of the tumor will result in a complete cure. Three of our six cases operated upon are still living and in good health; in one instance five and one-half years have elapsed since operation. One case has been lost sight of.

Metastases of the hypernephromata are not uncommon, although it was not observed in any of the cases of our series. In Case 1, there was a direct extension of the growth through the renal vein into the vena cava. The usual mode of metastasis is through the blood-stream by way of the renal vein, and this takes place usually in the later stages where there is extensive local invasion. The metastases, therefore, are found most frequently in the bones, lungs, and liver. Scudder (9) has recently recorded four instances of bone metastases and refers to eleven other cases in the literature, making fifteen in all, the majority of which were fatal. Rarely, extension may occur through the lymphatics. Stober (10) reports a case of hypernephroma of the left adrenal with metastases to the mediastinal lymph glands. I have been unable to find other similar instances in the literature.

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THE INFLUENCE OF THE REDUCTION OF KIDNEY SUBSTANCE UPON NITROGENOUS METABOLISM.[1]

BY RICHARD M. PEARCE, M. D.

This communication presents the results of one of several investigations having for their object the determination of the part played by chemical correlation, in a broad sense, in the productions of pathological conditions associated with diseases of the kidney.[2] In taking up such problems one of the first questions for consideration is that of the influence of the hypothetical internal secretion of the kidney upon general nitrogenous metabolism. I use the term hypothetical advisedly, for although this theory occupies a prominent place in the literature dealing with the question of uremia and is very suggestive, there is little experimental or other evidence to support it.

It was first brought to general notice by Brown-Sequard,[3] who as the result of his investigation of the internal secretion of the testicle came to very broad conclusions concerning internal secretions in general and stated that the kidney, as also other organs, have this function. He based his opinion as regards the kidney on clinical observation[4] and the study of dogs from which both kidneys had been removed as compared with those

[1] Aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Journal of Exper. Med.*, 1908, x, 632.

[2] Pearce, R. M., The Theory of Chemical Correlation as Applied to the Pathology of the Kidney, Annual Address before the Philadelphia Pathological Society, April 23, 1908.

[3] Brown-Sequard, Importance de la secretion interne des reins, *Arch. d. phys. norm. et path.*, 1893, v, 778.

[4] Fowler, E. P., Suppression of Urine, New York, 1881.

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in which the ureters had been ligated. As the result of both procedures the retention of metabolites is the same, but in the nephrectomized animals, death, which comes on more rapidly, is supposed to be due to the absence of an internal secretion which, it is assumed, is still furnished by the ligated kidneys. If, as he claimed, in the nephrectomized animals the internal secretion is replaced by the injection of renal juice, or glycerine extracts of kidney or by normal serum the animals live as long or even longer than those which have had both ureters ligated. Such observations are urged in support of the theory of internal secretion by those who do not believe uremia to be due to the retention of the products of metabolism.

Similarly, metabolism experiments on man which tend to show that uremia may occur without evident nitrogen retention are viewed in the same way and are taken by those who support the theory of internal secretion to indicate that uremia is not due to lack of elimination of metabolites but to loss of the internal secretion.

From the experimental side the only method of attack has been by the study of the variation in elimination of nitrogenous substances after extirpation of amounts of kidney substance sufficient presumably to disturb the hypothetical internal secretion. Upon this phase of the subject the observations of Tuffier, of Bradford and of Bainbridge and Beddard are available. Tuffier[5] removed first one kidney, and after an interval, a portion of the other. He came to the conclusion, based on ten experiments, that one and five-tenths gram of kidney substance per kilo of body weight was sufficient to maintain life and adds that except for oscillations due to the immediate effects of the operation no changes in the elimination of urine or urea were noted.

Bradford[6] also working with dogs, found that after the removal of approximately three-fourths of the total kidney weight death occurred in from one to six weeks from asthenia with great wasting; coma and convulsions were not observed. Death is apparently dependent on the amount of kidney substance removed and not upon mutilation inflicted by the surgi-

[5] Tuffier, T., Études expérimentelles sur la chirurgie des reins, Paris, 1889 (quoted from Bradford).

[6] Bradford, J. R., The Results following Partial Nephrectomy and the Influence of the Kidney upon Metabolism, *Jour. of Physiol.*, 1899, xxiii, 415.

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cal operation. Excision of a portion of one kidney or portions of both is followed by an increase in the volume of the urine, but unaccompanied by an increase in the total solids. After excision of three-fourths of the total kidney weight there occurs an increase in the amount of urea eliminated. This increase is absolute when appetite does not fail, and relative when little or no food is taken. Under the latter circumstances the amount of urea eliminated is as great as that excreted previously on a full diet. At the same time the blood and tissues, particularly the muscles, show a considerable increase in nitrogenous extractives. Bradford concludes that the disturbance of metabolism following the reduction of kidney substance is due, not to the retention of the products of normal destruction of tissue, but to an increased tissue catabolism especially of the muscles, producing large quantities of urea. He states that he has made no observations to determine whether this is due to the cessation of the action of a renal internal secretion. His results have, however, been so interpreted by later writers.

Bainbridge and Beddard[7] in a recent publication describe their observations on cats. They conclude that the removal of three-fourths of the kidney substance causes loss of appetite, wasting and death in a few days or weeks; that an increase of nitrogen in the urine is not constant and occurs only during the last few days of life when the animal has lost twenty-two per cent. or more of its body weight and therefore that the kidney has no direct influence on metabolism but that the increase of nitrogen is the result of inanition and similar to that which occurs in starving animals. They also found that there was not necessarily an increase in the volume of urine.

The difference of opinion between these investigators seemed sufficient to warrant a repetition of the experiments in order to determine the effect of the reduction of the kidney on nitrogenous metabolism. In carrying them out I have also investigated the total nitrogen eliminated in the feces in order to determine if possible whether or not the inanition could be explained by digestive disturbances due to faulty absorption

[7] Bainbridge, F. A., and Beddard, A. P., The Relation of the Kidneys to Metabolism, *Proc. Royal Soc.*, 1907, lxxix (B), 75.

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or possibly to the effect of irritating nitrogenous substances eliminated through the intestines.

These experiments were made upon dogs which were kept for some time before operation and during the entire course of the experiment in nitrogenous equilibrium. For this purpose a purin-free diet of casein, cracker dust and lard was used and the *per diem* amount of water limited to 600 cubic centimeters. The animals were kept in the usual well-ventilated metabolism cages and were catheterized at the end of each twenty-four hours. After each catheterization the bladder was washed out and the wash water added to the catheterized urine and that voided naturally and the whole made up to a definite volume. This urine was carefully preserved from changes of any kind until the analyses were made. When albuminuria caused the appearance of coagulable protein in the urine, which occasionally happened during a short period immediately following operation, this was removed by heat and acetic acid, the coagula being thoroughly boiled out with water and the washings added to the urine.

Upon these twenty-four samples the following determinations were made: Total nitrogen by the Kjeldahl method; ammonia by the Shaffer method and urea by the Mörner-Sjoquist method. The investigation was so delimited mainly because the changes in total nitrogen and in the elimination of urea and ammonia are the only points in dispute and in part on account of the negative nature of the results obtained by Bradford and by Bainbridge and Beddard in regard to other substances.

The general procedure was to place the animal in nitrogenous equilibrium, conduct control determinations for a period of three days, operate, and after allowing two or three days for recovery from the acute effects of the operation make determinations during one or more three day periods.

The operative procedure differed somewhat from that of the English investigators. Instead of removing a wedge of kidney substance the upper half of a kidney was removed and the bleeding from the cut surface controlled by a mattress suture. This method, although it narrows the pelvis somewhat, is not followed by infarction or hemorrhage and gives better results than that recommended by Bradford. At a subsequent operation either one-half the opposite kidney, or the entire kidney

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TABLE I.

(Dog 4, ¼ and ½ reduction.)

Date.	Urine.							Faeces.		Weight. Gms.	Notes.
	Amt. c.c.	Sp. Gr.	Total N Gms.	Urea. Per Gms.	Cent.	Ammonia. Per Gms.	Cent.	Total N. Gms.	Per Cent. N.		
Control Period.											
Oct. 21	525	1013	6.84	5.67	82.9	0.323	4.7	0.1285	3.0	13,780	
22	430	1017	6.45	5.35	83.0	0.320	4.9	0.1285	3.0	13,860	
23	545	1012	6.65	5.46	82.1	0.318	4.8	0.1285	3.0	13,840	
24	½ right kidney removed—wt. 25 gms.										
26	430	1016	8.25	7.09	86.0	0.338	4.1	0.1894	4.2	13,410	Albuminuria
27	430	1018	7.22	6.04	83.4	0.315	4.4	0.1894	4.2	13,400	
28	480	1014	7.81	6.53	83.5	0.293	3.8	0.1894	4.2	13,240	
Nov. 4	325	1020	6.69	5.62	85.5	0.231	3.5	0.2641	4.4	13,500	
5	440	1017	6.56	5.60	86.5	0.286	4.3	0.2641	4.4	13,770	Diarrhoea
6	430	1016	6.26	5.18	82.9	0.266	4.2	0.2641	4.4	13,610	
7	325	1018	5.25	4.34	82.6	0.240	4.6	0.2641	4.4	13,760	
8	460	1015	5.9	4.87	82.5	0.321	5.4	0.2641	4.4	13,840	Diarrhoea
8	½ left kidney removed—wt. 22 gms.										
20	410	1012	5.89	4.93	83.6	0.264	4.5	0.1765	3.07	11,810	
21	440	1013	5.65	4.83	85.6	0.291	5.1	0.1765	3.07	11,960	
22	510	1010	5.52	lost.		lost.		0.1765	3.07	11,930	100 c.c. extra water
Dec. 3	725	1008	7.14	6.14	85.9	0.343	4.8	0.6335 (?)	4.68	12,250	300 c.c. extra water
4	615	1009	6.39	5.31	83.1	0.298	4.7	0.6335 (?)	4.68	12,285	"
4	3d operation—death in 3 hours. Oedema of lungs.										

Weight of kidney removed at first and second operations.. 47 gms.
Weight of kidney found at autopsy..... 43.7 gms.

was extirpated and in the case of the former the remaining half of this kidney was taken out at a third operation. In some instances one entire kidney and half the opposite kidney were removed at one operation without any immediate ill effect. The present work includes metabolism studies on four dogs with varying degrees of kidney reduction, but a somewhat exhaustive study of the general effects of extirpation and of the process of repair in the kidney after various kinds of operative injury will be published later by Dr. J. A. Sampson and myself. At present it is sufficient to state that we have had no difficulty in keeping animals alive and in good condition without either general or local disturbances after

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TABLE II.

(Dog 21, ⅔ reduction.)

Date.	Urine.							Faeces.		Weight Grams.
	Amount c.c.	Sp. Gr.	Total N. Grams.	Urea. Gms.	Urea. Per Cent.	Ammonia Gms.	Ammonia Per Cent.	Total N. Grams.	Per Cent. N.	
Dec. 3		Rt. kidney (wt. 29 gms.) & ⅔ Lt. kidney (wt. 10 gms.)		Removed						8,410
17	440	1014	6.47	5.59	86.4	0.282	4.4	0.1806	4.34	8,210
18	437	1014	6.18	5.70	83.7	0.269	4.4	0.1806	4.34	8,230
19	435	1015	5.24	4.28	81.7	0.259	4.9	0.1806	4.34	8,225
Jan. 6		Killed								8,050

Weight of kidney removed at single operation..... 39 gms.
Weight of kidney remaining at autopsy..... 16.5 gms.

Total weight ..... 55.5 gms.

TABLE III.

(Dog 12, spontaneous nephritis, unilateral nephrectomy.)

Date.	Urine.							Faeces.		Weight Gms.	Notes.
	Amt. c.c.	Sp. Gr.	Total N. Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Total N. Gms.	Per Cent. N.		
Nov. 16	250	1031	6.55	5.04	77.2	0.276	4.2	0.1514	2.93	17,820	Alb. 4% Casts + + +
18	300	1028	6.71	5.39	80.4	0.290	4.3	0.1514	2.93	17,610	
19	212	1036	6.42	4.99	77.8	0.345	5.3	0.1514	2.93	17,520	
20	260	1034	6.66	5.22	78.4	0.362	5.4	0.1514	2.93	17,500	
22											Alb. 2½% Casts + + +
Dec. 6	Right kidney removed, weight 72 gms.							0.2058	3.58		Alb. 1½% o
10								0.1981	3.44		Casts + +
11	405	1017	7.80	6.05	77.6	0.335	4.29	0.1981	3.44	17,110	300 c.c. extra water
12	505	1015	6.44	5.23	81.1	0.313	4.86	0.2108	3.59	17,100	300 c.c. extra water
16								0.2108	3.59		
20	Died during operation on other kidney, which weighed 68 gms.									16,650	

the removal of one-quarter, one-half, and in some instances three-quarters of the total kidney substance at one operation. The removal of larger amounts and occasionally of three-quarters is followed by severe general disturbances which have rendered futile all attempts to maintain the animal in nitro-

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genous equilibrium. In one instance after removal of a considerable portion of the kidney substance, a nephritis developed, which added to the value of the experiment rather than otherwise.

TABLE IV.

(*Dog 13, 3/4 and 6/7 reduction; acute nephritis.*)

Date.	Urine.							Faeces.		Weight Gms.
	Amount c.c.	Sp. Gr.	Total N. Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Total N. Gms.	Per Cent. N.	
Nov. 2	Half left kidney removed, weight 14.5 gms.									15,840
13	Entire right kidney removed, weight 42 gms.									14,000
16	Nephritis. Alb. = ½ per cent. Abundant casts.			5.29		0.166		0.2125	5.53	13,100
21	410	1011	5.72		(?) 92.5		2.9			12,970
22	320	1016	4.78	4.84	80.2	0.251	5.2			13,070
23	375	1019	5.40	4.62	85.3	0.272	5.2			13,270
Dec. 3-5	Does not eat—more or less vomiting									
6	267	1016	3.61	2.87	79.5	0.143	4.0	0.0990	5.74	12,680
7	222	1020	3.04	2.43	79.9	0.119	3.9	0.0990	5.74	12,590
9	Eight gms. of remainder of left kidney removed.									
10-20	Gastro-intestinal disturbance—does not eat. Alb. 1½-2 per cent. Casts abundant.									
16								0.1766	6.66	
18	165	1016	1.89	1.56	82.5	0.040	2.1	0.0557	6.65	10,350
19	120	1017	1.47	1.24	84.4	0.028	1.2	0.0557	6.65	10,200
20	195	1008	0.689	0.437	63.4	0.527	7.6	0.0557	6.65	10,000
21	Chloroformed.									

Weight of kidney substance removed..... 64.5 gms.
Weight of remaining kidney..... 11 gms.

Total weight ..... 75.5 gms.

The results are shown in Tables I, II, III and IV. As a normal control period is given in one experiment only (Table I) a series of controls[8] are presented in Table V. These give the figures in six dogs fed on the same diet and kept under the same conditions as the dogs with kidney reduction. The averages only are given and are based on the figures of periods of three to five successive days.

Experiment I shows no appreciable changes in metabolism after the removal of one-half of one kidney or one-half of each kidney. The animal unfortunately died a few hours after the

[8] Taken from paper by Pearce, R. M., and Jackson, H. C., Experimental Liver Necrosis; III, Nitrogenous Metabolism, *Jour. Exper. Med.*, 1907, ix, 552.

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TABLE V.

Normal Dogs—Control.

Dog.	Total N. Gms.	Urea. Gms.	Urea. Per Cent.	Ammonia. Gms.	Ammonia. Per Cent.	Creatinin. Gms.	Creatinin. Per Cent.	Undetermined N. Gms.	Undetermined N. Per Cent.	Average of
		4.96		0.019		0.606		0.259		Five 24° periods.
A	6.35		78.1		7.9		9.5		4.1	
		3.24		0.128		0.278		0.108		Four " "
B	3.30		86.1		3.3		7.4		2.9	
		3.98		0.450		0.350		0.326		Four " "
C	4.10		78.4		8.8		6.7		6.0	
		5.39		0.395		0.345		0.568		Three " "
D	7.04		81.2		5.5		4.8		8.1	
		5.30		0.428		0.281		0.537		Three " "
E	6.56		80.7		5.8		4.2		7.9	
		5.61		0.364		0.354		0.213		Three " "
F	6.57		85.3		5.5		5.4		3.4	
		4.34		0.332		0.208		0.377		Four " "
G	5.36		82.0		6.7		3.9		7.4	
Average Per Cent.			81.7		6.2		6.0		5.7	

third operation with no lesions discoverable at autopsy except a very extensive edema of the lungs.

Experiment II indicates that the removal of two-thirds of the entire kidney substance at one operation does not interfere with the general condition of the animal as shown by the constant weight and normal metabolism figures.

The third experiment made on an animal with a spontaneous nephritis, a condition occasionally found in stray dogs, shows that this lesion has no effect on metabolism, even after the kidney substance is reduced one-half by a unilateral nephrectomy.

The fourth experiment was not planned for a study of metabolism, but when it was found that an animal with but one-quarter of its kidney substance had developed an acute nephritis, thus diminishing, it was assumed, the functional capacity of the fractional portion of the kidney remaining, it seemed too good an opportunity to lose and the animal was placed on a constant diet and the metabolism experiments carried out six days later. This animal, despite the great reduction of kidney substance and the presence of a nephritis, had a normal metabolism during the first three day observation period. Two weeks later, however, when appetite had begun to fail equilibrium was lost, although no change in the percentage relations of nitrogen was evident.

But after another period of two weeks had elapsed, and the

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kidney substance had still further been reduced by operation, leaving the animal with but one-seventh of its original kidney material, a change in the urea-ammonia ratio, indicative of inanition, occurred. That this final change is due, as Bainbridge and Beddard claim, to inanition there can be no doubt. Up to this point, the beginning of starvation, the changes in urea described by Bradford were not observed.

The discrepancy between these results and those of Bradford require a word of comment. Bradford, it will be remembered, found an increase of urea to occur with considerable frequency after removal of one-half or two-thirds of the kidney substance and almost constantly after removal of three-fourths. In the experiments here quoted the urea remained constant until the period of inanition. In my experiments exact twenty-four-hour samples of urine were obtained by catheterization, the animals were kept on a constant diet (casein, lard, cracker dust) and the more exact Mörner-Sjoquist method for the determination of urea was used. Bradford's estimations on the other hand were based on the amount of urine voided naturally in twenty-four hours; the diet (meat and biscuit) was weighed accurately but was administered according to the appetite of the animal; and the urea was estimated by the relatively inaccurate hypobromite method. The differences in methods explain, I think, the variance in results.

Creatinin estimations were not made in these experiments on account of the negative results obtained by Bainbridge and Beddard. The undetermined nitrogen was therefore not calculated, but if the averages for creatinin in normal dogs, presented in Table V, are taken as indicating the probable creatinin excretion and added to the urea and ammonia percentage it is found that the undetermined nitrogen does not in any instance, except in the dog with spontaneous nephritis (Table III) and in the later period of Dog 13 (Table IV), vary widely from the normal average of five and seven-tenths per cent. In this regard the nitrogen determination would therefore also appear to be normal. As far as the urine is concerned it would appear that no evidence is at hand to indicate that the kidney, through an internal secretion or otherwise, has any influence on general nitrogenous metabolism and I believe the theory of internal secretion in this regard at least may be set aside. There remains, however, the very important

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question of why the removal of more than three-fourths of the kidney substance leads to loss of appetite and consequent inanition. Although vomiting occasionally occurred in these animals it did not seem to be sufficiently frequent or severe to indicate a general gastro-intestinal disturbance. To test this point extirpation of the kidney was done on two dogs after the establishment of a gastric fistula. In this way it was hoped that the food necessary for nitrogenous equilibrium could be introduced artificially and by examination of both urine and feces some light might be thrown on the cause of the disturbance. These efforts were rendered futile, however, by the inability of the stomach to retain the materials introducd. The conclusion is inevitable therefore that although the kidney appears to have no direct influence on nitrogenous metabolism the removal of large portions of its substance does indirectly lead to disturbances of general nutrition by interfering apparently with the functions of the alimentary canal.

Examination of the Feces. The occurrence of serious gastric and intestinal disturbances in these animals after kidney reduction and their general similiarity to lesions occurring occasionally in man in the course of chronic nephritis led me, in view of our more recent ideas of the chemical control of the body and the influence of one secretion on another, so well brought out by Starling and Baylis's investigations, to study the feces of the animals in order to determine if partial nephrectomy had any influence on digestion, absorption or elimination into the intestine. Brainbridge and Beddard's claim that the disturbance in metabolism is due to inanition dependent on vomiting and diarrhea with eventual failure to take food and not to a direct influence of the kidney dodges the question. The point to be determined is whether or not the gastric and intestinal disturbances are caused by faulty absorption or by digestive disturbances due to the elimination into the intestine of products normally removed by the kidneys. The demonstration of such a relation would be important not only as an illustration of the chemical interrelationship between various organs, but would also aid in explaining similar disturbances associated with the nephritis of man.

These latter which, I understand, are frequently so severe as to present symptoms closely resembling a violent gastro-enteritis have been ascribed in part to alterations of the mucosa

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due to edema, and in part to the influence of the uremic condition on the central nervous system. While these explanations account for many of the symptoms, others, according to von Noorden,[9] must be attributed to toxic chemical action. In fact recent investigations show that in uremia substances usually eliminated by the kidneys are secreted vicariously into the alimentary tract. "Of these, the most irritating chemically is ammonia, which is formed in the intestine by decomposition of the secreted urea. It is also noticeable that the feces in uremic diarrhea are extremely rich in ammonia."

Studies of the feces having for their object the determination of the degree of absorption in nephritis, for which we are indebted mainly to von Noorden, show that the absorption of fats is very complete. The situation in regard to nitrogen is not so clear, the loss in some cases being greater than normal while in others an abnormally high percentage is found. The variation in some individuals, without a corresponding change in diet, or in the nature of the stools, or in the general condition and with no change in the percentage of dry substances or fat content of the feces, led von Noorden to the conclusion that the increase of nitrogen was due not to impaired absorption, but to the vicarious excretion of metabolites stored up in the organism. In many cases the excretion remained normal. High amounts, above three grams daily, were found in nephritis only in diarrhea (uremic) and were due largely to a high content of ammonium salts, constituting sometimes ten to twenty per cent. of the total fecal nitrogen.

In the four experiments tabulated above the total nitrogen in the feces evacuated during control periods and periods of metabolism study was estimated. The results as seen in the tables indicate no marked change in the total nitrogen or its percentage relation, except possibly in Experiment IV. In this animal with but one-seventh of its kidney substance, which after the first operation developed a severe nephritis, the *percentage* of nitrogen in the feces apparently shows a somewhat marked increase as compared with the other dogs. Unfortunately, no control figures on this animal are at hand. The low total nitrogen combined with a high percentage would appear to indicate the presence of substances of a higher nitro-

[9] Von Noorden, C., Metabolism and Practical Medicine (Vol. ii). Chicago, 1907.

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gen percentage content (*e. g.*, ammonia) than those normally present in the feces. This phase of the problem will be further investigated.

The inanition due to gastro-intestinal disturbance cannot therefore be explained by impaired absorption, or, except as possibly indicated by Experiment IV, by an undue elimination of nitrogenous substances. Irritation by increased elimination of toxic substances, non-nitrogenous in nature, may be a factor, but upon this point I have as yet no observations.

CONCLUSIONS.

1. The removal of one-half, two-thirds and sometimes three-quarters of the kidney substance in the dog causes no change in the general nitrogenous metabolism as determined by estimations of the total nitrogen, urea and ammonia elimination by the urine.

2. The removal of larger amounts, and sometimes of three quarters of the substance, leads to the metabolism condition of starvation. This, however, is apparently the result of the gastro-intestinal disturbance constantly associated with extensive kidney reduction and not of a disturbance of general nitrogenous metabolism.

3. The determination of the amount of fecal nitrogen indicates that the gastro-intestinal disturbance is not due to diminished absorption; and except in one instance there was no evidence of its being due to an increased elimination of nitrogenous substances into the intestine.

4. These experiments do not support the theory that the kidney furnishes an internal secretion having an important influence on general nitrogenous metabolism. At least, if such a function exists, it is not disturbed by the removal of three-quarters of the kidney substance.

5. The metabolism in excessive kidney reduction is that of inanition dependent on gastro-intestinal disturbances presumably due to faulty chemical correlation. In this connection further knowledge concerning the elimination into the intestines of toxic substances is desirable.

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CONCERNING THE PRESENCE OF NEPHROTOXIC SUBSTANCES IN THE SERUM OF ANIMALS WITH EXPERIMENTAL NEPHRITIS.*

By RICHARD M. PEARCE, M. D.
AND
H. P. SAWYER, M. D.

During the period of the active investigation of cytotoxic immune sera many attempts were made to utilize the results of the study of nephrotoxic sera in the explanation of various complications of chronic renal disease. It was assumed that if the injection into an animal of kidney parenchyma caused the appearance in the serum of that animal of a substance toxic, upon injection, for the kidney of another animal (heteronephrotoxin) it should be possible also to produce toxic substances in the serum of the same animal by so injuring its kidney as to cause degeneration of the renal cells. The production of such a serum (autonephrotoxin) by injuring one kidney, as by ligation of ureter, vessels, or entire pedicle, was attempted by several investigators, who claimed to be able to thus produce histological changes in the opposite kidney with the appearance of albumin in the urine. The serum of such animals also, it was claimed, had a similar effect if introduced into a normal animal of the same species (isonephrotoxin). Upon such experiments was based the theory that in chronic nephritis the continual degeneration of renal parenchyma was accompanied by an equally constant formation of autonephrolysin, the one dependent on the other, and that there was thus brought into play a vicious circle capable of explaining the course of this disease. Unfortunately for this and other theories based on similar observations, much of the early work on immune cytotoxins, on account of faulty methods, has been discarded; the theory of specificity has been set aside, and the observation concerning the production of autonephrotoxin by experimental ligation cannot be confirmed.

There is, however, a phenomenon brought out by the investigations along this line which remains unexplained and

* Work aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. of Med. Research*, 1908, xix, 269.

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which is of peculiar interest in connection with any discussion of the pathology of nephritis. This is the observation of Lindemann[1] that the serum of an animal suffering from an experimental chromate nephritis has the power to produce lesions of the kidney when introduced into a normal animal and also my own[2] observation of similar results when the serum of dogs with spontaneous nephritis, or of those with lesions due to nephrotoxic serum, as had also been noted by Bierry,[3] are introduced into normal dogs. Such injections cause the excretion of albumin and casts and histological changes in the kidney. These observations which, as far as I am aware, have never been questioned, indicate the presence in the serum either of a substance formed anew during a nephritis or an accumulation of toxic substances (metabolites) normally eliminated by the kidney. The phenomenon is quite distinct from that of the action of a substance produced by immunization, as it represents presumably the action of a substance or substances resulting from tissue destruction, or faulty function, or both. If found to be a constant attribute of the serum of experimental nephritis it is a matter of extreme importance in connection with the pathology of chronic nephritis. We have, therefore, largely on account of the interest of one of us in various problems of chemical correlation as applied to the kidney[4] re-opened the subject in the hope of determining upon what factors the observation in question rests.

Methods. From the outset the object of our investigation has been not so much the accumulation of positive evidence in support of this phenomenon as a thorough control study of the possibilities of error. As we have taken the appearance of coagulable protein in the urine as the criterion of kidney injury, we have attempted to control every other possible source of such protein. For this reason and because the phenomenon has been frequently quoted and generally accepted by writers on diseases of the kidney we present our methods

[1] Lindemann, W. Ueber| das Wesen der toxischen Nephritis. *Centralb. f. allg. Path. u. path. anat.*, 1900, xi, 308.

[2] Pearce, R. M. An experimental study of nephrotoxins. *Univ. of Penn. Bull.*, 1903, xvi, 217.

[3] Bierry, H. Recherches sur l'injection de sang et de sérums nephrotoxiques au chein. C. R. Acad. d. Sciences, 1901, cxxxii, 1145.

[4] Pearce, R. M. The theory of chemical correlation as applied to the pathology of the kidney. Annual Address before the Philadelphia Pathological Society, April 23, 1908.

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and results in considerable detail. As this study is largely a control investigation of a definite phenomenon and not of the methods of producing it, and as Bierry and Pearce are in accord concerning the action of the serum of an animal in which nephritis has been produced by a nephrotoxic immune serum, we have not repeated the experiments of the former, but have adopted, instead, Lindemann's simpler method of utilizing the serum of animals with chromate nephritis. A study has also been made of the effect of the serum of animals with uranium nephritis.

The demonstration of the possible toxic action of a serum on the kidney has been attempted in two ways; first by the examination of the urine after the injection of the serum of animals with experimental nephritis and second, the action of such serum, in vitro, upon renal cells. Dogs and rabbits were used. In experiments of the first type the urine was examined for several days or a week for albumin and casts. This is very important in both dogs and rabbits, but especially in the former on account of the frequency of spontaneous chronic nephritis. The animals which were to furnish the serum received injections of either potassium chromate or bichromate or of uranium nitrate. The former were given subcutaneously to rabbits in doses .03 gram and to dogs .06 gram daily or every other day, and the latter in like manner in doses of .0075 gram to rabbits and .015 gram to dogs. An estimation of the degree of kidney injury was obtained by daily examination of the urine. The animals were bled from the femoral artery after periods varying from two to five days. The serum thus obtained was injected into normal animals, always of the same species, as soon as possible after bleeding, usually within two to four hours, though occasionally on account of the slow separation of the clot, the serum stood over night before being used. The injections into rabbits were made into the ear vein without anesthesia. Dogs received the serum either in the abdomen without anesthesia or, after incision of the skin, in a small subcutaneous vein opposite the second joint of the hind leg under light ether anesthesia.

In these experiments the presence of coagulable protein and of casts in the urine has been taken as evidence of an influence of the serum upon the kidney. All possibilities of contamina-

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tion of the urine were avoided. The animals were kept in metabolism cages which were scrupulously cleaned daily and the food limited to dog biscuit, which could not readily become mixed with the urine. In those experiments with dogs in which the skin was incised before the injection the wound was carefully dressed in order to prevent oozing of blood or serum. Dogs developing a diarrhea, as occasionally happened, were discarded.

Owing to the almost constant presence of mucin in the dog's urine, as shown by Jackson and one of us[6] elsewhere, and the necessity of controlling this in the test for albumin, the following procedure was adopted: Four portions of absolutely clear filtered urine were placed in test-tubes; the first served as control, to the second acetic acid only was added, to the third acetic acid and potassium ferrocyanide solution ,and the fourth was heated and acetic acid then added. The amount of acid added to each tube was always the same and approximately the same quantity urine was used daily. By this method the clouding or precipitate due to mucin was, we think, accurately controlled. This clouding of normal dog's urine by the presence of mucin may be expressed thus o, +, +, +. This we have taken as a normal standard and when clouding in both third and fourth tubes has been greater than that in the second we have considered it evidence of the presence of protein, and the degree of clouding we have indicated by multiplying plus signs.

The centrifugalized sediment of the urine has been examined with special regard to the presence of casts, renal cells, and red and white blood corpuscles.

Results. Eight dogs received the serum of dogs with chromate nephritis. Of these four were injected intravenously. In one, receiving the serum in dose of one cubic centimeter to five hundred and seventy-eight grams of body weight, no change in the urine occurred. In a second and a third, doses of one to four hundred and ninety-three and one to three hundred and fifty respectively, a trace of protein was present in the urine on the day following the injection. In the latter of these a few finer granular casts, renal cells, and leucocytes

[6] Pearce, R. M., and Jackson, H. C. Concerning the production of cytotoxic sera by the injection of nucleo-proteids. Jour. Infect. Dis., 1906, iii, 742.

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were found in the sediment. The fourth experiment is given in detail, as follows:

Dog 61.—February 28, female, weighing fifteen thousand three hundred thirty grams, placed in metabolism cage.

February 29 to March 3, urine contains no albumin and sediment is negative.

March 3, received in small vein of leg under light ether anesthesia, thirty-two cubic centimeters (dose 1 to 480) of serum of chromate dog.

March 4, cage urine (seventy cubic centimeters, Sp. Gr. 1034) contains a considerable amount of coagulable protein which unfortunately was not estimated. Sediment shows numerous fine fat globules and cells of the type of renal cells and a few polymorphonuclear leucocytes; no casts, no red blood corpuscles. Urine from bladder at 11 a. m. amounts to seventy cubic centimeters with a specific gravity of 1020 and contains five-tenths per cent. protein by the Esbach method. Sediment contains numerous cells of renal type and a few leucocytes. Urine from bladder at 3 p. m., sixteen cubic centimeters in amount, Sp. Gr. 1034, protein two and five-tenths per cent., sediment unchanged.

March 5, cage urine amounts to one hundred fifty-four cubic centimeters, specific gravity is 1042 and Esbach method gives two and five-tenths per cent. protein; sediment as on the fourth. Urine from bladder at 9 a. m. contains but a trace of protein with elements of sediment fewer in number.

March 6, protein twenty-five hundredths per cent., sediment contains few renal and pus cells but no casts.

March 7, ditto.

March 8, urine, one hundred sixty-five cubic centimeters, specific gravity 1038, color amber, protein twenty-five hundredths per cent., sediment contains a small number of renal cells and leucocytes and fat globules and for the first time a few finely granudar casts.

March 9 and 10, protein and sediment as on the eighth.

March 11, two hundred and seventy-five cubic centimeters of urine, specific gravity 1029, protein in traces which cannot be estimated by Esbach. Sediment negative except for an occasional leucocyte.

March 12 to 15, urine normal. Weight of dog on March 15 fourteen thousand four hundred twenty grams.

In order to control the possible toxic action of ether on the kidney and also any accidental admixture of protein to the urine, by oozing of blood or serum from the incision over the injected vein, four dogs received serum injected directly into the peritoneal cavity without ether and without incision. The dose varied from one to two hundred and eighty-seven to one to four hundred and ninety. In all of these the injection was immediately followed by the appearance in the urine for a period of two to five days of traces

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of protein and small numbers of finely granular casts, but in none was the amount of protein equal to that in the urine of dog 61 previously described. The following experiment is typical of this group:

Dog 63.—February 28, male puppy, weighing four thousand nine hundred and seventy grams, placed in metabolism cage. February 29 to March 3, urine normal. Results of tests for protein give the mucin reaction (0, +, +, +). Sediment negative.

March 4, ten cubic centimeters of chromate serum (dose 1-490) injected into peritoneal cavity.

March 5, protein tests, 0, +, 3+, 3+; sediment; few renal cells and leucocytes; no casts.

March 6, protein tests ditto, sediment as above with addition of a few finely granular casts.

March 7, no urine.

March 8, as on sixth.

March 9, 10, and 11, urine normal.

It is worthy of note that the lesions produced were not as severe or as constant as those described by Lindemann.

The experiments with uranium serum include one dog injected intravenously and four intraperitoneally. The intravenous injection (dose 1:1000) was followed by an elimination of casts without albuminuria. The casts were present in small numbers and were of a finely granular type with an occasional hyaline or epithelial cast and a few renal and white blood cells. The casts appeared on the first and third days after injection and could not be found on the fourth and fifth days. Casts had not been present in the preliminary examination covering a period of six days.

On account of the peculiar result of this experiment the animal was injected intraperitoneally on the fifth day. The same serum, which had been kept on ice, was used (in the dose of 1:370). Casts of the finely granular and hyaline types and renal cells and leucocytes reappeared in the urine for two days, but no protein could be detected.

Of the three experiments in which uranium serum was injected intraperitoneally, one (dose 1:408) was negative and the other two (doses 1:400 and 1:635) showed a transient elimination of small amounts of coagulable protein with, in one, a few hyaline and finely granular casts and in the other no casts.

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Although these experiments with dogs give a fair proportion of positive results, a small number of similar experiments with rabbits were absolutely negative. Three rabbits received uranium serum and two chromate serum in doses of five to twelve cubic centimeters (1:110 to 1:350) with no change whatever in the urine.

Although this investigation has to do mainly with the effect of the serum of experimental nephritis, the detection in the course of our routine examinations of several instances of spontaneous nephritis has permitted the testing of such serum. In an earlier communication, one of us[1] describes the occurrence of albuminuria with the elimination of casts in three of seven dogs receiving such serum intravenously. Of the present experiments, two in number, one confirms this earlier experience. The serum of a dog with spontaneous nephritis, eliminating from two to five per cent. protein and an abundance of casts throughout the month during which it was under observation had a definite nephrotoxic power (in the dose of 1:210). The serum of a second dog with a less severe nephritis had no effect in the same dose.

The occurrence of spontaneous nephritis in the rabbit was observed but once. An animal eliminating .5 to 1.25 per cent. protein daily was bled and its serum injected in doses of ten cubic centimeters (1:150) into two rabbits with no effect.

In three instances dogs with spontaneous nephritis were utilized in another way. It occurred to us that if the serum of an experimental nephritis has a toxic action on a normal kidney it might have the power to aggravate an existing spontaneous nephritis. One of these dogs therefore was injected, intravenously, with uranium serum (dose of 1:400) and a second with chromate serum, intraperitoneally (dose of 1:460), but without effect on the elimination of protein or casts. In a third experiment of this type a dog weighing nine thousand ten grams, with a very severe nephritis, received at the same time forty cubic centimeters of uranium serum, intravenously, and twenty cubic centimeters in the abdomen, without result.

A word may be said about another phase of this subject. Bierry and also Pearce have shown, apparently conclusively, that the serum of a dog suffering from a nephritis caused by

[1] Pearce, R. M., and Jackson, H. C., loc. cit.

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a heteronephrotoxic serum (prepared by injecting the rabbit with dog's kidney) has a definite nephrotoxic power when injected into the blood stream of a second dog. We have not repeated these experiments, but in the course of our work on another problem we found it necessary to procure the reverse type of immune nephrotoxic serum, that is, one toxic for the rabbit's kidney (prepared by injecting rabbit's kidney into the dog). This serum had a definite toxic action on rabbit's kidney, but the serum of rabbits so treated when injected into normal rabbits (dose 1:100 to 1:200) had no nephrotoxic effect, as is the case in the dog.

It is noteworthy that by no method of experimentation have we been able to demonstrate a nephrotoxic action of the serum of rabbits with kidney injury.

The question arises as to whether the toxic action of the serum of an experimental nephritis in the dog may be due, not to some peculiar substance developing as the result of injury to kidney cells, but to metabolites retained as the result of imperfect kidney function. We have performed no experiments, such as the injection of the serum of animals with complete nephrectomy, to test this point, but have found that the serum of animals with experimental reductions of the kidney substance to one-fourth the normal amount has no effect on the kidney of normal dogs. This conclusion is based on experiments with the sera of two dogs, the serum of one obtained one month and of the other two months after extirpation of three-quarters of the kidney substance. Thirty cubic centimeters of the first serum was injected in a dog weighing five thousand four hundred forty grams and thirty-two of the latter in a dog six thousand grams in weight. In neither did protein or casts appear in the urine.

The power of the serum of experimental nephritis to agglutinate renal cells in vitro was tested with seven sera. A mixture of renal cells in salt solution was prepared from the washed kidney, and to one-half cubic centimeter lots in test-tubes were added five cubic centimeters of each of the sera to be tested. Cell mixtures and sera were used within a few hours after they were obtained. Observations were made every hour for six hours. As a control, normal dog serum was used. Three sera of dogs with uranium, three with chromate, and one with spontaneous nephritis were tested in this way. In

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no instance did agglutination occur, and the degree of precipitation did not differ from that of the control. No difference in cell structure could be detected by microscopic examination.

In so far as this method of testing may be of value these results point to the absence of an isonephrotoxic activity of the serum of experimental nephritis and the results are not in accord with those obtained by injecting the same sera into the living animal.

In addition to the various methods of control which we have described, there is naturally the question of the elimination by the kidney of an excess of protein injected into the blood stream. In view of the fact that the injections have always been made into an animal of the same species and also that the amounts injected have been comparatively small, this factor could be set aside at once if it were not for a curious observation of Weiss.[6] This investigator as the result of a very extensive series of experiments came to the conclusion that all foreign sera cause albuminuria of some degree, but that homologous sera do not except when the serum of one sex is injected into the opposite sex. His evidence on the latter point, however, rests on a single experiment in which traces of protein resulted from injecting the serum of a male into a female rabbit and his quotation of Favaret's single observation of a like result upon injecting the serum of a bitch into a dog. In our control experiments we have kept this point in mind, but have not been able to confirm it. In the dog, injections of normal dog serum in doses as high as one to three hundred, and in the rabbit of normal rabbit serum in doses of one to one hundred and fifty have failed to produce albuminuria, irrespective of the sex of the animal furnishing or receiving the serum. As we have always used homologous sera, the toxic effect of an alien serum does not come into question.

We have also controlled the possibility of a periodic albuminuria in the dog. For this purpose four dogs were set aside, and the urine of each examined daily for periods of ten days to two weeks. In none was albuminuria found nor were casts present during this time. Each gave the mucin reaction but nothing more. During this period two of these dogs

[6] Weiss, O. Ueber die Wirkungen von Blutserum-injectionen im Blut. Arch. f. d. Ges. Phys., 1896, lxv, 215.

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were etherized and small quantities of blood taken from the jugular vein without any effect on the urine. These latter served therefore as controls also of our operative procedure.

The possibility of carrying over in the serum minute amounts of the salts injected must be considered. Attempts to detect, by the usual tests, the presence of chrome and uranium salts in the filtrate of the serum concentrated after coagulation have failed. Such tests, however, are not very sensitive and it is possible that traces may have been present. If present, the amount must have been so minute that it seems very improbable that they could have anything to do with the lesion described. Certainly they appear to have had no effect in the experiments with rabbits, and on this evidence alone we feel justified in ruling out the possibility of carrying over these salts in the serum.

In addition to the various controls described, we have by careful selection and elimination ruled out the possibility of an admixture to the urine of protein substances from local inflammatory conditions, as balanitis in the dog, or lesions of the uterus or vagina in the bitch. The surface of the entire body as well as the mouth of each animal has also been carefully examined for lesions capable of allowing a discharge of blood or serum. As the food has been limited to dry dog biscuit and the cage carefully screened to prevent particles dropping into the collecting bottle, we believe the presence of protein from the food can be ruled out.

In short, we have investigated every possible source of error which suggested itself, but have been unable to explain the presence of albumin in the urine except by a toxic action of the serum on the kidney.

CONCLUSIONS.

The positive results here described confirm the observation of Lindemann, Bierry, and Pearce that the serum of dogs with various types of nephritis has a toxic action on the kidney manifested by the appearance, for a short time, of protein and casts in the urine.

A very complete series of control observations offer no explanation for the appearance of protein other than as the result of injury to the kidney.

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It has not been possible to demonstrate a nephrotoxic power for the serum of rabbits with experimental nephritis and it is therefore manifestly improper to assume that this nephrotoxic power is a constant characteristic of the serum of all animals suffering from nephritis.

For this reason, although the phenomenon observed is suggestive and worthy of investigation on a larger scale, it should be utilized with caution in any theoretical explanation of the pathology of chronic nephritis.

A STUDY OF EXPERIMENTAL REDUCTION OF KIDNEY TISSUE WITH SPECIAL REFERENCE TO THE CHANGES IN THAT REMAINING.[1]

By JOHN A. SAMPSON, M. D.
AND
RICHARD M. PEARCE, M. D.

The following experiments in reduction of kidney tissue in dogs were undertaken in order that one of the writers might study the influence of such reduction on nitrogenous metabolism[2] and also for the purpose of determining the effect of this procedure on the remaining kidney tissue and upon the general condition of the animal.

The scanty literature of the subject may be briefly reviewed as follows:

The most extensive series of kidney reduction is that of Bradford.[3] The operative procedure of this investigator was to remove from the middle of the kidney, entering the pelvis, a wedged-shaped mass of kidney substance. This mass was equal to one-quarter to one-half of the entire kidney. After a variable period of time the entire opposite kidney was removed. In some instances a wedge was taken from each kidney and later the remaining tissue still further reduced. Of a total of thirty-three dogs, four died after the first operation and six at or shortly after the second operation. Of the twenty-three surviving the second operation, eight lived a considerable period of time and were

[1] Aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Exper. Med.*, 1908, x, 745.

[2] Pearce, R. M., The Influence of the Reduction of the Kidney Substance on Nitrogenous Metabolism, *Jour. of Exper. Med.*, 1908, x, 632.

[3] Bradford, J. R., The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, *Jour. of Physiol.*, 1899, xxiii, 415.

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killed in good health. The effect on the kidney of the first operation was usually atrophy of the organ. This occurred also if both kidneys were operated upon. After the second operation no serious disturbance of health occurred but a variable amount of wasting, usually transitory, was the rule.

If two-thirds of the kidney was removed death usually followed while the loss of three-quarters rendered survival impossible, death occurring usually in one to six weeks, from asthenia and great wasting.

Bradford found that two grams of kidney tissue per kilo of body weight was sufficient for maintenance of life (normal ratio 6.7 grams). Tuffier[4] gives 1.5 grams, Paoli[5] states that one-half a kidney is necessary. The latter found the operation to be followed frequently by hypertrophy of the glandular epithelium, dilatation of the vessel and a new formation of glomeruli and tubules. Tuffier's operation differed from Bradford in that he removed one entire kidney first and later a portion of the other. As a result of ten experiments he found no permanent disturbance of the urine and no effect on the development of growing animals.

Von Haberer's[6] experiments on three goats and thirty-eight dogs are most unsatisfactory because many of his animals died of pneumonia. He practiced very extensive resections within very short periods of time and showed that it is possible for a dog to survive the removal of one kidney and one-third of the other at a single operation or one and a half at two operations within a week. The mortality was very high.

Passler and Heineke[7] in their work on experimental heart hypertrophy, practiced extreme kidney reduction; they followed Bradford's method, allowing an interval of four weeks between the first and second operation; in five dogs cachexia and death followed. In eighteen surviving the second operation, at intervals varying from a few days to eleven months, a third, fourth, fifth or sixth operation was done, at each a small portion of kidney substance being removed. All finally died, from operations, accident or cachexia. As their interest was chiefly in heart hypertrophy, the details of the effect of reduction on the kidney tissue remaining are not given.

Bainbridge and Beddard,[8] working with cats according to Bradford's method, reduced the kidney substance three-quarters. This caused loss of appetite, wasting and death in a few days or weeks. Descriptions of the effect on the remaining kidney tissue are not given.

METHODS.

As our operative procedure differed from that of the other investigators it is here given in detail. If only one kidney

[4] Tuffier, T., Etudes expérimentales sur la chirurgie du rein, Paris, 1899 (quoted by Bradford).

[5] Paoli, Della resezione del rene *Cent. f. Chirurgie*, 1892, xix, 78.

[6] V. Haberer, H., Experimentelle Untersuchungen über Nierenreduktion und Funktion des restierenden Parenchyms, *Mitteilungen a.d. Grenzgebieten d. Med. u. Chir.*, 1907, xvii, 57.

[7] Passler and Heineke, Versuche zur Pathologie des Morbus Brightii, *Verhandl. d. Deutsch. path. Gesellsch.*, 1905, ix, 99.

[8] Bainbridge, F. A., and Beddard, A. P., The Relation of the Kidney to Metabolism. *Proc. of the Royal Soc.*, B, 1907, lxxix, 75.

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was operated upon, it was exposed through a so-called "gridiron" incision in the lumbar region by separating the muscle fibers and not cutting them. If both kidneys were exposed at one operation, this was done transperitoneally through a median abdominal incision. In the first few experiments the pedicle of the kidney was compressed by an assistant while the upper pole was excised and then the bleeding was controlled by mattress sutures of catgut and silk passing through the entire kidney substance and the upper portion of the pelvis. Later it was found easier to place catgut sutures first as shown in Figs. 1 and 2, tie them and excise the upper pole, the operation usually being bloodless, and possible without an assistant.

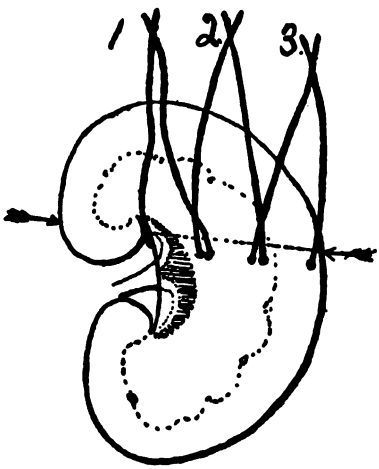

Fig. 1

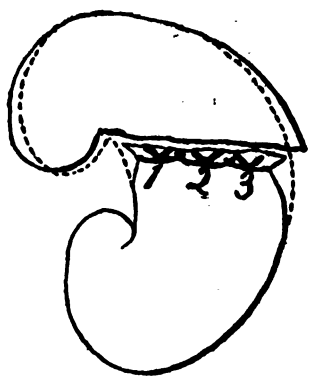

Fig. 2

FIG. 1. Technique of resection of upper pole of the kidney.

By means of a straight needle with a dull point, three interlacing mattress catgut (No. 2 Cumal) sutures (1, 2 and 3) are first passed through the kidney in a line which approximately divides the kidney in half (see illustration). Care must be taken to avoid injuring the ureter and for this reason the line of sutures is taken a little obliquely rather than straight across the kidney. These sutures are then tied, thus completely shutting off the blood supply to the upper pole. The upper pole is cut off from two to four millimeters beyond the sutures as indicated by the arrows.

FIG. 2. Immediate result of resection of upper pole of the kidney.

The dotted line indicates the original outline of the upper pole. After excising it, the base of the upper pole flares apart and the segment is thus lower and wider than before the operation. The sutures 1, 2 and 3 have been tied, thus constricting the upper portion of the remaining

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kidney tissue and by making the capsule more tense the part of the kidney, left behind, is a trifle smaller than before the operation.

This operative procedure we have considered preferable to that of Bradford and other investigators because there is a minimum disturbance of the blood supply of the kidney tissue remaining. The infarcted tissue, which results from the injury, and must be absorbed, lies at one pole of an otherwise intact kidney while in the experiments of Bradford and others, it is centrally located and thus possibly disturbs the nutrition of the entire organ. Our method furthermore permits of a more accurate estimation of the amount of kidney reduction in that the degree of reduction is represented by the part excised plus that outside of and that in the immediate neighborhood of the sutures. Histological examinations of kidneys from animals dying shortly after operation have shown that the zone of necrosis rarely extends more than one-half centimeter from the sutures into the remaining kidney tissue. By the other method, after the removal of a wedge-shaped piece of tissue from the midst of the organ, the sutures necessary to approximate the parts remaining and to control bleeding of necessity destroy a mass of kidney tissue which in proportion to that excised must be much greater than that destroyed in removing one pole. By our method a portion of the pelvis is necessarily removed and there is some danger of interfering with the flow of urine into the ureter. By proper care we have found that this can be avoided.

Except for the animals used for the metabolism studies above mentioned, the dogs were fed on dog biscuits, and did not have any exercise other than that possible in fairly roomy cages. The general condition of the animals was determined by observations in regard to appetite and weight.

All material obtained at operation or autopsy was preserved in ten per cent. formalin. No subdivisions of this material were made but large sections were obtained which represented the entire mass. By this method it was possible to study in one section, cortex, pyramid, pelvis and reparative or other changes in the field of operation. By superimposing these large sections it was possible to compare directly the remaining kidney tissue with that removed at operation and also to make tracings for comparison and illustrations.

Our experiments are sixteen in number, of which two (one

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death from anesthesia and another from hemorrhage shortly after operation) are excluded. The remaining fourteen experiments are divided into four groups.

GROUP I. REMOVAL OF UPPER POLE OF ONE KIDNEY.

No. 1 (Dog 40).

Operative Procedure.—January 23, 1908. Under ether narcosis, the upper pole of the left kidney was removed as shown in Figs. 1 and 2. The length of the left kidney was five and six-tenths centimeters and the portion remaining outside of the sutures was two and seven-tenths centimeters. At the same time the right kidney was exposed and measured.

Termination.—Killed on the twenty-second day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 11,020 to 9,710 grams.

Effect on Remaining Kidney Tissue.—Slight but definite atrophy. Healing is perfect, the renal tissue, compressed by the sutures, is replaced by fibrous tissue except for a small area of infarcted tissue corresponding to vessels showing obliterated endarteritis. In the fibrous tissue adjacent to the pelvis there is a small area of new bone formation. Otherwise the renal tissue is normal. The opposite kidney is apparently unaffected by the operation.

No. 2 (Dog 41).

Operative Procedure.—January 23, 1908. Under ether narcosis, the upper pole of the left kidney was removed. The length of the left kidney was six centimeters and the portion remaining outside of the sutures was three centimeters. At the same time the right kidney was exposed and measured.

Termination.—Killed on the thirty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 13,610 to 10,960 grams. Four weeks after the operation the urine contained a considerable amount of coagulable protein with numerous finely granular and fatty casts, pus and epithelial cells (urine was not examined before operation).

Effect on Remaining Kidney Tissue.—Very slight if any atrophy. Healing is perfect except for a few areas of necrotic tissue near the pelvis. In the scar there is an area of calcified tubules. Pelvic epithelum is greatly thickened and penetrates the underlying scar tissue, forming alveolar masses of epithelial cells.

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Otherwise the renal tissue is normal. Opposite kidney is apparently unaffected by the operation.

No. 3 (Dog 31).

Operative Procedure.—December 31, 1907. Under ether narcosis, the upper pole of the right kidney was removed. The length of the right kidney was six and two-tenths centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters. At the same time the right kidney was measured.

Termination.—Killed on the forty-eighth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 10,620 to 9,650 grams. Urine, on the fourth day, was normal but at the time of autopsy contained coagulable protein and pus cells, but no casts.

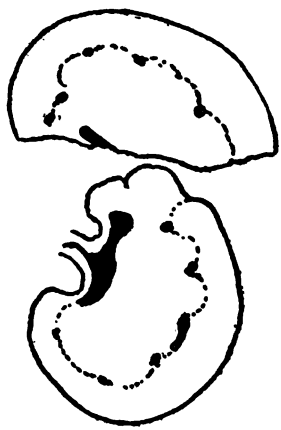

Fig. 3

FIG. 3. Tracings of sagittal sections of portions of a kidney, one portion removed at operation and the other at autopsy on the thirty-fifth day.

The upper pole was removed at operation as indicated in Figs. 1 and 2 and shows the characteristic flaring apart of the segment removed. The lower portion was removed at autopsy and has apparently atrophied but, by comparing it with a similar tracing of the opposite kidney and even from the measurements taken at the close of the operation (see Fig. 2), there is very little if any atrophy except in the tissue destroyed by the sutures and replaced by scar tissue. For description of microscopical findings see Experiment No. 2.

Effect on Remaining Kidney Tissue.—Very slight if any atrophy exists. Healing is perfect. There is dilatation of the pelvis of the kidney with a chronic pyelitis and thickening of the

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epithelium, and extensive bone formation immediately beneath this epithelium. Calcified tubules are present in the scar tissue. Otherwise the renal tissue shows atrophy of glomeruli with fibrous thickening of Bowman's capsule and extensive round cell infiltration of both cortex and pyramid. The tubules in places are dilated and in other places compressed. The portion of kidney removed at operation and the opposite kidney shows a spontaneous chronic nephritis but less marked than that just described.

GROUP II. REMOVAL OF UPPER POLE OF EACH KIDNEY AT ONE OPERATION.

No. 4 (Dog 65).

Operative Procedure.—March 7, 1908. Under ether narcosis, the upper pole of each kidney was removed. The length of the right kidney was four and five-tenths centimeters and the portion remaining outside of the sutures was two and three-tenths centimeters. The length of the left kidney was four and four-tenths centimeters and the portion remaining outside of the sutures was two and six-tenths centimeters.

Termination.—Died on thirtieth day.

General Effect.—Post-operative history was uneventful until the last week, when the animal refused food, lost weight rapidly and died on the thirtieth day.

Effect on Remaining Kidney Tissue.—No change in the size of the portion of the right kidney remaining. Healing was perfect except for a small area of necrosis along the line of suture, thickening of epithelium of pelvis and isolated masses of proliferating epithelium in the scar tissue. Otherwise the remaining renal tissue is normal.

The pelvis of the left kidney is filled with calculi, one occluding the lumen of the ureter. Associated with this there is an ulcerative pyelitis with abscesses involving the pelvic fat and lower portion of the pyramid. Where pelvic epithelium is intact it shows hyperplasia. There is no definite atrophy of cortex and pyramid.

No. 5 (Dog 66).

Operative Procedure.—March 7, 1908. Under ether narcosis, the upper pole of each kidney was removed. The length of the right kidney was four and nine-tenths centimeters and the portion remaining outside of the sutures was three centimeters.

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The length of the left kidney was four and eighth-tenths centimeters and the portion remaining outside of the sutures was two and six-tenths centimeters.

Termination.—Killed on the fifty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 4,620 to 4,340 grams.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the right kidney remaining. Healing is perfect. There is moderate thickening of the epithelium of the pelvis. Renal tissue is normal.

There is no change in the size of the portion of the left kidney remaining, and it is similar to the right kidney.

No. 6 (Dog 1).

Operative Procedure.—May 23, 1907. Under ether narcosis the upper pole of each kidney was removed. The length of each kidney was six centimeters and the portion remaining outside of the sutures was three centimeters. Weight of portion of right kidney removed was ten grams and of left eleven grams.

Termination.—Died on one hundredth and sixty-fourth day, from general peritonitis, the fifth day after the removal of the remaining portion of the left kidney when the peritoneal cavity was opened and soiled with infected urine.

General Effect.—Post-operative history was uneventful. The dog was in the country during the summer and became pregnant. The weight at the time of the first operation was 13,180 grams; at the second operation (pregnant) 16,010 grams and after death with the uterus empty (aborted just before death) it was 12,110 grams.

Effect on Remaining Kidney Tissue.—Left kidney weighed eighteen grams, length four and eight-tenths centimeters, an increase of one and eight-tenths centimeters. There was a small calculus in the pelvis about a silk suture. Healing is perfect, kidney has assumed its normal shape and except for the presence of a silk suture it would be difficult to distinguish it from a normal kidney. Microscopically there is evidence of pyelitis.

Right kidney weighed twenty-eight grams, length five and one-tenth centimeters, an increase of two and one-tenth centimeters above the portion remaining beyond the sutures at operation. Healing is perfect, microscopically renal tissue is normal. There is bone formation beneath the epithelium of the pelvis.

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GROUP III. REMOVAL OF ONE KIDNEY AND UPPER POLE OF THE OTHER AT ONE OPERATION.

No. 7 (Dog 35).

Operative Procedure.—January 23, 1908. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six centimeters and the portion remaining outside of the sutures was three and two-tenths centimeters.

Termination.—Killed on the sixth day (dying).

General Effect.—There was persistent vomiting after operation with gradual loss of strength, and failure to eat; a small amount of urine was passed daily.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney remaining. Extensive areas of infarction about the sutures are present with widespread calcification of the tubules. Infarcted area is one and five-tenths centimeters wide, the line of sutures being in the middle of this area. Abscess formation present about sutures.

No. 8 (Dog 69).

Operative Procedure.—April 6, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was five and seven-tenths centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters.

Termination.—Killed on the seventh day (dying). Cause of death not apparent.

General Effect.—Refused food and vomited persistently until killed on the seventh day. There was a loss of weight from 9,710 to 9,620 grams. Urine was voided after operation but was not examined.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. The area of infarction and hemorrhage is one and seven-tenths centimeters broad, the line of sutures being in the middle of this area. Very slight leucocytic infiltration about the sutures is present. There is marked proliferation of the pelvic epithelium.

No. 9 (Dog 24).

Operative Procedure.—December 9, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six and three-tenths

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centimeters and the portion remaining outside of the sutures was three and five-tenths centimeters.

Termination.—Died on the tenth day.

General Effect.—Ate poorly, lost 500 grams in the first five days after the operation, hematuria.

Effect on Remaining Kidney Tissue.—There is no change in the size of the remaining portion of the left kidney. Infarcted area varies from one to one and three-tenths centimeters, the sutures being nearly at the junction of the normal and necrotic tissue. Otherwise the kidney is normal.

No. 10 (Dog 21).

Operative Procedure.—December 3, 1907. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left was five and two-tenths centimeters and the portion remaining outside of the sutures was less than half the original length of the kidney.

Termination.—Killed on the thirty-fifth day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 8,410 to 8,050 grams. Slight albuminuria and pyuria.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect; a few calcified tubules are present in the scar tissue. Otherwise kidney tissue is normal.

No. 11 (Dog 72).

Operative Procedure.—March 21, 1908. Under ether narcosis the right kidney was removed and the upper pole of the left. The length of the left kidney was six centimeters and the portion outside of the sutures was three and two-tenths centimeters.

Termination.—Killed on the forty-first day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 15,060 to 12,340 grams. Urine obtained from bladder at autopsy was normal.

Effect on Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect; there are a few calcified tubules in the scar tissue. As compared with portion excised at operation and the opposite kidney there is no change in the renal tissue. Each show a chronic process characterized by round cell infiltration.

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No. 12 (Dog 71).

Operative Procedure.—March 21, 1908. Under ether narcosis, the right kidney was removed and the upper pole of the left. The length of the left kidney was five and four-tenths centimeters and the portion remaining outside of the sutures was three centimeters.

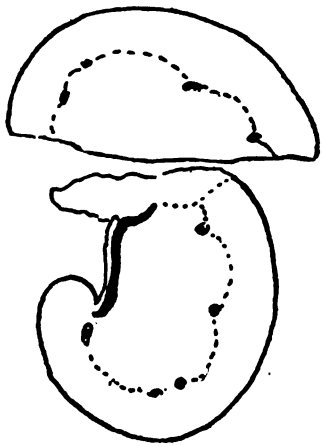

Fig. 4

FIG. 4. Tracings of sagittal sections of portions of a kidney, one portion removed at operation and the other at autopsy on the forty-first day. For description of gross appearance see Fig. 3 and for description of microscopical findings see Experiment No. 11.

Termination.—Killed on the fifty-seventh day.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 8,010 to 6,060 grams.

Effect of Remaining Kidney Tissue.—There is no change in the size of the portion of the kidney tissue remaining. Healing is perfect, there are a few calcified tubules in the scar tissue, as in No. 11.

GROUP IV. REDUCTION OF KIDNEY TISSUE BY MULTIPLE OPERATIONS.

No. 13 (Dog 4).

Operative Procedure.—October 24, 1908. Under ether narcosis the upper pole (over $\frac{1}{2}$ approximately $\frac{2}{3}$) of the right kidney was removed. November 8, 1908. The upper pole of the left was removed. The length of the left kidney was six and

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five-tenths centimeters and the portion remaining outside of the sutures was three centimeters. December 11, 1908. The remainder of the left kidney was removed.

Termination.—Died four hours after the last operation from œdema of the lungs.

General Effect.—Post-operative history was uneventful. There was a loss of weight from 13,826 to 12,250 grams and there were periodic albuminuria and pus cells.

Effect on Remaining Kidney Tissue.—There is slight if any atrophy of remaining portion of right kidney. Healing is perfect. A cheesy material containing calculi is present in the pelvis; bone formation in scar tissue beneath the pelvic epithelium; marked hyperplasia of pelvic epithelium. Kidney tissue is normal except for areas of round cell infiltration, also present in portion excised at first operation.

No change in the size of the remaining portion of the left kidney. Healing is perfect with extensive bone formation beneath the pelvic epithelium. In the pelvic fat there is a small abscess about one of the sutures. Otherwise tissue is as in the opposite kidney.

No. 14 (Dog 13).

Operative Procedure.—November 2, 1907. Under ether narcosis the upper pole of the left kidney (weight fourteen and five-tenths grams) was removed. The length of the left kidney was six and two-tenths centimeters and the portion remaining outside of the sutures was two and seven-tenths centimeters. November 13, 1907. The right kidney was removed (weight forty-two grams). December 9, 1907. A segment one centimeter thick was removed (weight eight grams) from the lower pole of the remaining portion of the left kidney.

Termination.—Died eleven days after the last operation.

General Effect.—Good recovery from each operation except the last. More or less vomiting after the last operation, albuminuria one half to two per cent., abundant casts; voided urine until death and averaged 180 cubic centimeters for the last three days. There was a loss of weight from 15,840 to 10,000 grams.

Effect on Remaining Kidney Tissue.—The portion of the left kidney found at autopsy showed distinct atrophy and weighed eleven grams. Based on the weight of the normal right kidney this represents fourteen per cent. of the original kidney tissue. Healing from the first operation is perfect and site of second

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operation is occupied by a mass of necrotic tissue extending into the pelvis and surrounded by purulent fluid. Microscopically there is evidence of an acute ulcerative pyelitis with slight pyelonephritis and extensive cast formation in the tubules. Otherwise kidney tissue is normal.

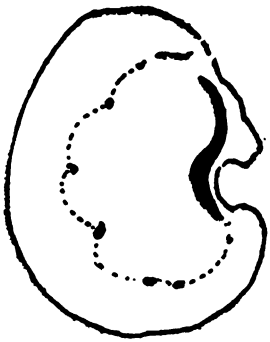

Fig. 5

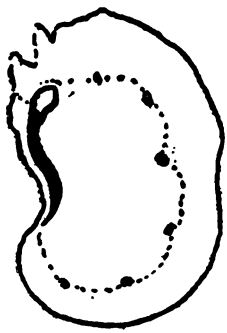

Fig. 6

FIG. 5. Tracing of sagittal section of portion of the right kidney remaining, 164 days after removal of the upper pole.

The upper pole was removed as indicated in Figs. 1 and 2.

The portion remaining shows distinct hypertrophy and the thickening of the cortex is most evident near the field of the operation. See Experiment No. 6.

FIG. 6. Tracing of sagittal section of the portion of the left kidney remaining, 159 days after removal of the upper pole.

The upper pole was removed as indicated in Figs. 1 and 2.

This is from the same dog as the kidney shown in Fig. 5 the hypertrophy is not as marked as in the other kidney but the thickening of the cortex near the field of operation is more marked and the kidney has almost resumed its normal contour. A calculus about a silk suture is present in the upper portion of the pelvis.

GENERAL SUMMARY.

The immediate effect of the operation on the portion of the kidney remaining is an infarction of the tissue compressed by the sutures. This area of necrosis extends but a short distance into the adjacent kidney tissue. The infarcted tissue gradually becomes replaced by fibrous tissue and in three to four weeks' time the necrotic tissue entirely disappears. The amount of fibrous tissue in time becomes so slight and the healing so perfect that it is difficult to detect the site of the operation. The renal elements sometimes persist in the infarcted area and the glomeruli apparently are more resistant than the tubules. The

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tubules in the infarcted area sometimes become calcified and bone formation beneath the epithelium of the pelvis is of very frequent occurrence. The pelvic epithelium usually shows marked proliferation and may invade the field of operation in alveolar masses. Calculi may form in the pelvis of the kidney. Sutures penetrating the pelvis as well as the necrotic tissue resulting from the compression of the sutures probably furnish the nuclei for the calculi.

Removal of approximately half of one kidney did not alter either the remaining portion of that kidney or the size of the opposite kidney in two animals of this series. These experiments were terminated on the thirty-fourth and forty-seventh days. In a similar experiment of twenty-one days' duration there was slight but definite atrophy of the remaining tissue of the kidney operated upon.

Removal of approximately half of each kidney at one operation did not alter the remaining kidney tissue in two animals of the second group. The longest period of observation was fifty-four days. On the other hand in a similar experiment where 164 days elapsed, the remaining portions of each kidney had increased markedly in size.

Removal of one kidney and approximately half of the other did not alter the remaining kidney tissue in six animals in which from five to fifty-six days elapsed before termination of the experiment.

In six experiments in which one kidney was removed and approximately half of the other, three of the animals died as a result of the operation on the sixth, seventh and tenth days. The probable cause of death was renal insufficiency; the animals refused food, vomited persistently and lost strength and weight. The other three animals recovered and were killed at periods varying from five to eight weeks. The reduction of the kidney tissue to one-quarter of its original amount at one operation was attained with danger but was not necessarily fatal.

In every experiment there was a loss of weight varying from four to twenty-four per cent. To what extent this loss in weight is due to the reduction of kidney substance and to what extent it is due to diet and confinement it is impossible to say, as we made no control experiments to elucidate these points.

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THE RELATION OF LESIONS OF THE ADRENAL GLAND TO CHRONIC NEPHRITIS AND TO ARTERIOSCLEROSIS; AN ANATOMICAL STUDY.[1]

By Richard M. Pearce, M. D.

This investigation has for its object the determination, as far as may be possible by anatomical study, of the relation which exists between arteriosclerosis and changes in the adrenal gland on the one hand, and between chronic interstitial nephritis and adrenal lesions on the other.

The problem is of considerable general interest at the present moment in view of the numerous recent publications of French clinicians on this subject and has attracted my attention in connection with a recent critical study of the theory of chemical correlation as applied to the kidney.[2] It would appear natural, in view of our knowledge of the pressor effect of adrenalin and of the experimental lesions produced in the rabbit by this substance, as well as of our knowledge of the frequent association of hypertension with chronic interstitial nephritis and arteriosclerosis, to associate both the renal and arterial disturbances with some alteration of the adrenal. These suggestive facts, taken in connection with the rapidly accumulating evidence of intimate chemical correlation between widely separated organs, renders the problem an exceedingly interesting and suggestive one.

Within the past three years French investigators, led by Vaquez, have contributed a large mass of literature which indicates that localized or diffuse hyperplasia of the adrenal is commonly associated, when the disease does not run too rapid a course, with contracted kidney and arteriosclerosis. The hyperplasia is considered as an indication of hyperactivity of the antitoxic and angiotonic functions of the gland, what we might call perhaps hyperadrenalism.

The literature of this subject is now so voluminous that it would be unwise to review it completely, especially as the anatomical studies have been recently very completely collected and

[1] Work aided by a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Exper. Med.*, 1908, x, 735.

[2] Pearce, R. M., The Theory of Chemical Correlation as Applied to the Pathology of the Kidney. Annual address before the Philadelphia Pathological Society, April 23, 1908.

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described by Rose,[3] and the somewhat scanty and not very convincing experimental studies have been similarly treated by Darré.[4] To indicate, however, the observations upon which this theory is based a portion of the earlier literature should be given briefly:

The first case described by Vaquez was one of adenoma of the cortex of the adrenal associated with a contracted kidney. Josué described three instances of diffuse arteriosclerosis with hypertrophy of the adrenal. Aubertin and Ambard studied eight cases in which there was contracted kidney and found fatty adenoma in three, diffuse hyperplasia in four and in the remaining case with a rapid clinical course a normal adrenal. Lemaire in a single instance, and Froin and Rivet in six out of seven cases of nephritis found adenomata or nodular hyperplasia; the remaining patient, in whom the rise in blood pressure was slight, had a normal adrenal. Menetrier found two adenomata in seven patients with contracted kidney. These figures indicate the frequency with which pathological changes have been described in the adrenals in association with renal and vascular lesions. There are many negative findings however and the frequency of similar lesions with diseases other than those of the kidney and vascular system have not been sufficiently investigated. On the other hand Landau[5] who has examined the adrenals of sixteen individuals, suffering from general arteriosclerosis between the ages of forty-nine and ninety-six years found no changes which might not be ascribed to the effect on the gland of arteriosclerosis of the vessels of the adrenal itself.

In the hope of throwing more light on the subject by purely anatomical studies I have examined the autopsy records of the Bender Laboratory and have attempted to determine the relation of vascular and nephritic lesions to changes in the adrenal. Attention has been paid also to the occurrence of hyperplasia of the adrenal in association with conditions other than chronic vascular or renal disease.

It has not been an easy matter in all instances, on account of the slighter variations so common in the adrenal, to establish a dividing line between a "normal picture" and the changes in the gland considered by the French writers to be characteristic of chronic interstitial nephritis. An arbitrary normal standard was finally established by comparing the descriptions of several histologists with sections of the adrenal of twelve individuals

[3] Rose, F., Blutdrucksteigerung, Schrumpfniere und Nebennieren, *Med. Klinik*, 1907, iii, 1405.

[4] Darré, H., De l'influence des altérations du rein sur les glandes surrénales, Paris, 1907.

[5] Landau, H., Ueber die anatomischen Veränderungen in den Nebennieren bei Arteriosklerose, *Zeitschr. f. klin. Med.*, 1907, lxiv, 227.

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between the ages of forty and fifty-six years who had met death by violence and were free from chronic disease of any kind, and whose glands were therefore presumably normal for the ages given. The validity of the establishment of this normal picture was further strengthened by the study of glands of forty-six individuals under thirty years of age dying as the result of various acute infectious diseases. In this way the more acute degenerative changes were controlled.

On the other hand the descriptions of Aubertin and Ambard[6] and of Vaquez and Aubertin[7] have been taken as depicting accurately the changes deemed by the French writers to be characteristic of chronic interstitial nephritis with hypertension. Their histological descriptions may be summarized as follows: The earliest lesion is a "non-fatty" nodule of the glomerular zone involving to some extent the fascicular zone. This change may be found in other conditions, but is more marked in chronic interstitial nephritis. Another early appearance is a "fatty" nodule well limited and isolated in the midst of normal cells and seen especially in the fascicular zone. The latter may sometimes be very numerous and not sharply limited. The final stage is a *hyperplasia adenomatosa totale* with definite increase in the weight of the gland. A true macroscopic adenoma of the adrenal they state to be of no significance, unless associated with diffuse hyperplasia. It differs from the so-called adenoma of nephritis in that the latter is a more marked or accentuated local manifestation of a diffuse process, while the ordinary macroscopic adenoma develops in an otherwise normal gland.

It must be here stated that these writers have never limited these lesions to the adrenal of chronic interstitial nephritis but have said, that if individuals of very advanced age are eliminated, the lesions are found in nineteen of twenty cases of the interstitial type of nephritis and but once in twenty cases of the parenchymatous type, or in other diseases than interstitial nephritis. They do insist, however, that these lesions are always accompanied by hypertension except in those cases of chronic nephritis running a very rapid course.

The material of the present study consists of 163 adrenals

[6] Aubertin, C., and Ambard, L., Lésions des capsules surrénales dans les néphrites avec hypertension, *Bull. et mem. d. l. soc. med. h. hôp. d. Paris*, 1904, xxi. 175.

[7] Vaquez and Aubertin, C., Sur l'hyperplasie surrénale des néphrites hypertensives, *ibid.*, 1905, xxii, 705.

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which have been divided into groups according to the ages of the individual and the presence or absence of chronic renal and vascular lesions. They were selected from a group of 1,200 autopsies and include all sections of the adrenal which pass through the center of the entire gland and are well preserved and well stained. They are therefore representative of the lesions occurring in the average run of autopsy material. In no case, however, have we notes of the blood pressure during life. For this reason the study of material of this kind is not comparable, strictly speaking, to the studies of the French investigators as the latter, for the most part, used only material from individuals who during life showed definite hypertension. The purely anatomical studies here presented are, however, of value as control observations and form a basis for a detailed study, now in progress, of the adrenal from individuals exhibiting hypertension clinically.

Group I. Normal Glands.—This group includes twelve glands from individuals between forty and fifty years of age (average forty-four years) who met sudden death from some form of violence. They are taken as normal controls.

Group II. Glands from Individuals under Thirty Years of Age Dying of Infectious Diseases.—This group includes forty-seven glands of which fourteen are from infants and sixteen from children. They were taken as controls of the acute degenerative or other lesions which might be caused by infection. The diseases represented are diphtheria, typhoid fever, tuberculosis and noma, acute infections of the respiratory system, and diseases of the gastro-intestinal tract, middle ear, and uterus. In only eight examples could departures from the normal structure be found. These occurred in three glands of general tuberculosis, in two of typhoid fever, and one gland each of diphtheria, pelvic abscess and septic endometritis. All were in individuals over twenty years of age. In one gland of the tuberculosis group, a diffuse hyperplasia of the fascicular zone with the characteristic spongy appearance, and in another a very definite nodular hyperplasia of the glomerular zone occurred; in two excessive pigmentation and in all a hyperplasia of the medulla existed. In one also a slight diffuse increase of connective tissue was present and in another some round cell infiltration. In the case of acute septic endometritis a very definite hyperplasia of the medulla with round cell infiltration existed. In one gland from a case of typhoid fever were noted focal necroses with extensive leuco-

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cytic infiltration and in the other multiple nodular hyperplasia of the glomerular and fascicular zones and diffuse hyperplasia of the medulla. In the glands from cases of diphtheria and pelvic abscess nodular adenomata were also present with more or less diffuse "fatty" changes. In connection with the changes in the adrenals of tuberculosis individuals here described it is noteworthy that Aubertin and Clunet[8] have described hyperplasia of the medulla in five cases of tuberculosis.

Group III. Glands from Individuals Over Thirty Years of Age, Free of Chronic Vascular and Renal Disease.—This group includes nineteen glands from individuals between thirty-one and fifty-seven years of age (average forty-four years). They are to be regarded as controls for the glands derived from individuals of the arteriosclerotic period. Eight showed no adenomatous changes, while in eleven were found the changes described by Vaquez and Aubertin. The hyperplasia was nodular in eight, diffuse in three and combined in two; in three of the nodular variety the lesion was of the "fatty" type. Increase of connective tissue was found in three glands from cases of syphilis, tuberculosis and cancer, respectively, with, in the first, considerable round cell infiltration. Excessive pigmentation was present in two glands of chronic mitral endocarditis. Hyperplasia of the medulla occurred in two instances in association with syphilis and chronic mitral disease, an association which has also been noted by Aubertin and Clunet.

Group IV. Glands from Individuals Over Thirty Years of Age, with Contracted Kidney, Arteriosclerosis and Heart Hypertrophy.—This group has been very carefully selected and comprises twenty-four glands from individuals who suffered from typical chronic nephritis of the interstitial type (contracted kidney) associated with well-marked general arteriosclerosis, involving the aorta or its larger branches, and with hypertrophy of the left ventricle (in four instances both ventricles) of the heart. That is, it represents the anatomical material corresponding to the typical clinical features of chronic vascular and renal disease with which hypertension is usually associated. The ages varied from thirty-eight to eighty-seven years (average, fifty-nine years).

Only one of these glands could be considered absolutely nor-

[8] Aubertin, C., et Clunet, J., Hypertrophie cardiaque et hyperplaise médullaire des surrénales, *C. r. Soc. de Biol.*, 1907, lxiii, 595.

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mal. Sixteen showed changes which must be considered as the result of the effect on the gland of the arteriosclerotic changes in its own vessels. These changes are similar to those found in the kidney, pancreas and other organs when their vessels are altered by arteriosclerosis. The vessels of the medulla and capsule show fibrous and hyaline thickening with diminution of lumen, the capsule is thickened and both cortex and medulla show various grades of connective tissue increase and round cell infiltration.

In all instances, in addition to these productive changes, certain lesions described by the French writers were present to some degree, and most frequently the diffuse hyperplasia combined with simple nodules of either the "fatty" or "non-fatty" type.

Similar hyperplastic lesions were found in the seven glands in which evident fibrous and local vascular changes were absent, though in three of them, it should be noted, round cell infiltration was a prominent condition.

In six glands of this group a definite hyperplasia of the medulla was apparent, and in two pigmentation was very marked; in almost all the glands it was greater than normal.

The relation of the adenomatous changes to the local lesions due to arteriosclerosis, in the sixteen glands first described, might be explained as compensatory to gland injury and analogous to the "multiple nodular hyperplasia" seen in the liver in cirrhosis and in repair of acute yellow atrophy or after other destructive lesions. This explanation cannot on the other hand be applied to the simple hyperplasia observed in the seven glands without connective tissue proliferation. The hyperplasia, however, is no more frequent in these glands than in Groups II and III in which chronic vascular and renal lesions do not come into question.

Group V. Arteriosclerosis Associated with Chronic Nephritis of the Parenchymatous Type.—This group includes thirteen glands from individuals who showed arteriosclerosis of the same grade as the previous group, but in whom chronic parenchymatous nephritis instead of the interstitial type existed. This material was very carefully selected in order to exclude the latter and to include examples of general vascular lesions of the same degree as in the latter disease. The ages varied from thirty-eight to eighty years (average, fifty-seven years).

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Of these glands two were normal, five showed vascular and connective tissue lesions of the character seen in Group IV, associated in three with hyperplasia, and six showed hyperplasia only.

The conditions therefore are not essentially different from those of the previous group and do not support the view of the greater importance of chronic interstitial nephritis as productive of hyperplasia of the adrenal.

Group VI. Arteriosclerosis without Chronic Nephritis.—This group comprises sixteen glands obtained from individuals with well-marked arteriosclerosis of the aorta and larger vessels but without chronic nephritis of any type. The fatalities include various infections and the chronic diseases common to the latter half of life. The ages vary from thirty-five to seventy-four years (average, fifty years).

Of the sixteen glands, ten showed the vascular and connective tissue changes previously described as characteristic of the arteriosclerotic gland. In all but three of these, adenomatous lesions also exist. Four exhibited hyperplasia only, and two were normal.

These observations compared with those made of Groups IV and V indicate that the constant factor in producing the hyperplasia is arteriosclerosis; and hyperplasia occurs indifferently in chronic nephritis of the parenchymatous type, of the interstitial type, and in absence of chronic nephritis of all types.

Group VII. Chronic Nephritis without Arteriosclerosis.—This group includes twelve glands obtained from individuals without arteriosclerosis but who had definite chronic nephritis, which in ten was of the parenchymatous and in two of the interstitial type. Incidentally this group bears on the question of the frequency with which chronic interstitial nephritis occurs in the absence of arteriosclerosis. The ages ranged from twenty-three to fifty years (average, thirty-six years).

Five of the glands were normal. Two, from individuals with pneumonia and gangrene of the leg, respectively, showed diffuse hyperplasia with discrete non-fatty nodules; and four showed nodular adenomata only. The remaining gland from an individual with tertiary syphilis presented very extensive round cell infiltration of the medulla, but no hyperplasia. Extensive round cell infiltration was present also in the gland from an individual

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with gangrene of the leg; and slight infiltration in one of chronic mitral disease. In no instance was an increase of connective tissue present. Of the two cases of interstitial nephritis one gland showed nodular hyperplasia and the other none.

These findings are in accord with those previously presented as far as the influence of chronic nephritis of the interstitial type is concerned and indicate, as do the findings in Groups II and III, the relative frequency of hyperplasia of the adrenal in the absence of arteriosclerosis.

Group VIII. Does Hyperplasia Occur in Chronic Destructive Lesions of the Adrenal?—In another section (Group IV) the statement has been made that the adenomatous hyperplasia of the adrenal, in chronic productive lesions of the gland, might be in part a compensatory process analogous to the nodular hyperplasia occurring in the liver of cirrhosis. An attempt has been made to determine whether such a hyperplasia occurs in the persisting tissue of adrenals which are the seat of extensive chronic destructive processes. Two glands invaded by carcinoma, two with amyloid and ten with tuberculosis have been studied. In two of these, cancer and amyloid respectively, a nodular hyperplasia of the "non-fatty" type was demonstrable in the glomerular and fascicular zones, while in four of the tuberculous organs areas were found which could be interpreted only as the result of hyperplasia. These masses do not show the normal architecture of the adrenal, but are atypical and consist of very large pale vacuolated cells usually containing considerable pigment. The masses are located, frequently, at a distance from the tuberculous lesions and encased in connective tissue. In one gland in which considerable portions of the organ remained intact a diffuse hyperplasia was present.

These findings support the theory of a compensatory nodular hyperplasia of the adrenal, and suggest a possible explanation of the relatively constant hyperplasia of the arteriosclerotic gland.

Group IX. Macroscopic Adenoma of the Adrenal and Kidney (Hypernephroma).—Although Vaquez and Aubertin state that macroscopic adenomata are of no importance in the production of hypertension or in the relation of the adrenal to chronic nephritis, I have grouped these cases in order to present the subject in complete form.

Three hypernephromata of the kidney and three adenomata of

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the adrenal were available for study. One of the latter was from an individual of thirty-eight years of age who was free from renal and cardio-vascular lesions. The other five were all from individuals between fifty and sixty years of age. Chronic nephritis of the parenchymatous type was present in two and of the interstitial type in two individuals; and the kidney was normal in one individual. In three of the cases a well-marked general arteriosclerosis and in two slight lesions of the aorta and coronary arteries existed. Heart hypertrophy was absent in all.

Macroscopic adrenal adenomata would therefore appear to have no definite relation to chronic interstitial nephritis; whether they bear any relation to arteriosclerosis cannot be concluded from the small number of examples in my studies.

SUMMARY.

Vaquez and Aubertin advance three theories in explanation of the adrenal hyperplasia; first, that it may not be the cause of hypertension but "an antitoxic hyperplasia" caused by the retained products of metabolism which may be responsible also for the hypertension; second, that it may be the cause of hypertension but secondary to the renal lesion; third, that it may be the cause of hypertension but may antedate the renal lesion or be entirely independent of it. They, as well as other French writers, insist that this hyperplasia is almost constantly associated with chronic nephritis of the interstitial type and it is seldom found with the parenchymatous type of nephritis, or with other lesions.

Hyperplasia of the adrenal, as far as my material enables one to judge, does not occur during the first and second decades. In the third decade it is relatively frequent in the absence of chronic arterial and renal disease but reaches the maximum in association with such disease after the fourth decade. It is an almost constant lesion in arteriosclerosis associated with chronic interstitial nephritis and left-sided heart hypertrophy, but occurs with almost equal frequency in arteriosclerosis with chronic nephritis of the parenchymatous type. It is a relatively frequent lesion of arteriosclerosis without chronic nephritis and of the latter without arteriosclerosis also. As the result of this analysis one is lead to the view that while hyperplasia of the adrenal is a very frequent concomitant of chronic renal and arterial disease it is not exclusively a feature of either type of nephritis or yet of chronic

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vascular disease; but it probably represents the effect of some factor operating in that period of life in which chronic renal and arterial affections are most frequent.

Worthy of special emphasis is the observation that the characteristic lesion of an adrenal, the seat of local arteriosclerosis, is of the type of the chronic productive inflammation seen in arteriosclerosis of the pancreas and kidney; that is, thickening of the vessels, increase of connective tissue and round cell infiltration. Associated with these changes is a hyperplasia which is very constant, and which may be, in part, of the nature of a compensatory hyperplasia similar to that seen in the liver of cirrhosis and acute yellow atrophy. A hyperplasia of this type, as has been shown, may occur in destructive lesions of the gland. This, however, does not explain hyperplasia in the absence of local vascular changes which fact is, possibly, as suggested by Landau, evidence, not of a correlation between kidney and adrenal, but of a vicarious hypertrophy depending upon lesions of some other organ of the body than the kidney, possibly some other ductless gland, affected by arteriosclerosis or other disease.

CLINICAL NOTES AND PHYSICOCHEMICAL STUDY OF SALT ELIMINATION IN THE URINE OF AN INDIVIDUAL WITH GENERAL EDEMA OF OBSCURE ORIGIN, FOLLOWED BY CURE.*

By HOLMES C. JACKSON, Ph. D.
AND
ARTHUR W. ELTING, M. D.
Albany, N. Y.

This case of general edema of obscure origin without evidence of kidney lesion is reported in part on account of its interest clinically and in part because of the unusual importance of the results of the physical and chemical examination of urine. Incidentally, therapeutic observations difficult of interpretation but apparently of some value are also presented.

* This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association, and is from the Bender Laboratory, Albany, N. Y.

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CLINICAL REPORT (A. W. ELTING).

Patient. G. H. R., aged 45, an experimental chemist by occupation, was first seen in July, 1907, at which time he complained of irritation of the throat, general debility, and inability to concentrate his attention on his work.

History. His family and past history were negative, except that for the last ten years most of his time had been spent in a much vitiated atmosphere due to the decomposition at high temperatures of linseed oil, gums, resins and hydrocarbon compounds. These vapors are for the most part acid, readily form metallic salts, and are as a rule irritating to the urinary tract. The patient used alcohol and tobacco moderately and gave an indefinite and improbable history of chancre twenty years ago, with no subsequent luetic manifestations.

Onset of disease. He had noticed for several years past that when subjected to the fumes above described he would be troubled by irritation of the urinary tract and of the throat. During the winter of 1903 he first observed an occasional swelling of the palmar surface of the fingers, and about the same time some slight enlargement of the upper part of the abdomen. He also became fatigued on slight exertion and very languid. Moderate doses of blue mass relieved these conditions temporarily. In 1905 the feeling of lassitude became quite constant. He would arise in the morning feeling fairly well, but on moving about would soon become tired. He was also troubled with drowsiness during the day, sometimes falling asleep at his desk. Nervousness was an almost constant symptom, for which no definite cause could be assigned, and he suffered from slight lapses of memory and was at times much troubled with a cough. On retiring at night he would fall asleep for a short time and then awaken with a nervous start which would be followed by insomnia for the rest of the night. In April, 1907, he noticed some puffiness about the lower eyelids, which later extended to the temporal region. About this time he found that he could not lie with his head low in bed without experiencing a sensation in the ears similar to that caused by water. When the patient was seen in July there was very slight puffiness about the lower eyelids and face, with moderate chronic laryngitis, but no other evidence of physical disorder. The usual urine examination at that time was negative. In August and September the edema increased somewhat in the face and extended to the neck, chest, upper part of the back and the upper extremities. He was seen again about October 1, 1907, at which time the edema in the above-mentioned localities was quite pronounced and there was slight dyspnea and cyanosis. A suspicion of mediastinal tumor was entertained, but absolutely no physical evidence of such a condition could be detected. The urine examination was negative (chlorid elimination was not tested). The patient was advised to give up his work for a time and go to his home in Pennsylvania. This he did. About this time the cough became much aggravated and more paroxysmal in character, accompanied by vertigo and semi-unconsciousness for a few seconds. The patient also found it impossible to lie flat in bed because of dyspnea and was compelled to sleep propped up.

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About October 15, 1907, the attacks of coughing became much more severe and breathing more labored; the expectoration was slight in amount and consisted of a frothy mucus. The edema gradually extended downward over the trunk, then involved the scrotum and finally, but gradually, the legs. The patient's condition became desperate because of the attacks of coughing, the dyspnea and the cyanosis, and with much difficulty he was brought from his home in Pennsylvania to St. Peter's Hospital, where he was admitted October 30, 1907.

Condition on Admission. This was alarming. Dyspnea was very marked and increased on the slightest exertion. Cyanosis was pronounced and there was a most extensive edema of the face, neck, chest, back and upper extremities, less marked over the lower part of the trunk, the scrotum and lower extremities. The patient suffered from frequent paroxysms of coughing, and at these times he would have mild convulsive seizures and become unconscious for a few seconds. It was impossible for the patient to lie down and he sat propped up in a chair. The edema was of a firm character and seemed to involve the muscles and deeper tissues rather than the subcutaneous tissues.

Physical Examination. There was absolutely no evidence of any accumulation of fluid in the serous cavities. Examination of the heart and lungs was negative except for sibilant, sonorous and some small moist râles. The abdominal viscera were normal. The temperature was subnormal and the pulse about 100. The quantity of urine was much reduced, varying from 300 to 500 cubic centimeters in twenty-four hours. The patient was extremely nervous and slept but little. His appetite was poor. The blood examination was negative. Satisfactory radiographs of the thorax were obtained, but these were normal and there was no evidence whatever of mediastinal tumor or aneurism. Nervousness was a constant and pronounced symptom, as was insomnia. The patient's condition for the first week after admission to the hospital was most desperate, chiefly because of the attacks of dyspnea and coughing, during which he would frequently lose consciousness. The appetite was very poor.

Treatment. On admission to the hospital the patient was given large quantities of liquids and iodid of potash in increasing doses.

November 10: The administration of acetate of potash and infusion of digitalis apparently caused some increase in the volume of urine.

November 12: A steam bath was given without any evident increase in the perspiration, the patient's skin having been unusually dry at all times and perspiration evidently very much below the normal. Heroin in one-twelfth grain doses seemed to be quite effectual in relieving the cough. He was unable to lie down and spent all his time propped up in a chair.

November 21: He suffered a very severe attack of dyspnea and became unconscious. Oxygen, amyl nitrite and nitroglycerin were freely used and resuscitated him. The patient was given an ounce of magnesium sulphate every other morning and the stools were quite watery in consequence.

November 25: He was placed on as nearly a salt-free diet as could be

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secured, and from this date until February 1, 1908, a somewhat complete quantitative examination of the urine was performed daily, the results of which follow the clinical report.

November 27: The diuretic mixture was discontinued.

December 8: The patient was given potassium nitrate in fifteen grain doses every three hours. As the result of the administration of this the volume of the urine increased until on December 12 it amounted to 3,225 cubic centimeters (Table 2). Coincident with this there was a marked diminution in the edema and a decided improvement in the general condition. Attempts were also made to give the patient subcutaneous infusions of sterile water, but these had to be abandoned because of the great pain they occasioned. He was, however, given twelve ounces of sterile water by rectum each day. The potassium nitrate was discontinued on December 12 and was resumed on December 14, with but little effect on the volume of the urine, but the chlorid output was markedly increased.

December 13: The patient was given an artificial Nauheim bath and this was repeated on two successive days with apparently a marked softening and lessening of the edema and a decided improvement in the cough and dyspnea.

December 27: Another series of artificial Nauheim baths was given on alternate days with a lessening of the edema. About this time the patient was able to assume a somewhat reclining posture at night and gradually as his condition improved his position in sleeping approached more and more the horizontal. About January 1, 1908, the patient began to take a few steps, but was easily exhausted and was very weak.

January 4: He experienced a very severe attack of coughing and dyspnea and the edema increased slightly.

January 20: A small fixed quantity of salt, 5 grams per diem, was added to the food, but the patient objected strongly, stating that it nauseated him. Gradually, however, he became accustomed to it and the dislike for salt disappeared.

Clinical Course. The course of the edema was variable; as a rule, when the urine increased the edema decreased. The edema first disappeared from the chest, then the face and the back, the legs and forearms being the last to yield. Gradually the patient was encouraged to take more exercise and to get out of doors for a short time each day. This seemed to exert a very beneficial effect on the edema, and the dyspnea and coughing seemed to vary with the edema.

Later Course. The patient left the hospital on February 1, 1908. At this time there was still some edema in the forearms and legs, and some dyspnea, which increased on exertion. His general condition was fairly good. His strength was greatly improved and he was voiding about a normal amount of urine. He was then able to sleep in the horizontal position and was decidedly less nervous. The week following discharge from the hospital was spent at his home. The urine varied from 600 to 900 cubic centimeters in twenty-four hours, and the patient's appetite was somewhat improved. At the end of one week he started for Bermuda. The sea air increased the cough and expectoration somewhat, but the

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breathing was less labored. Shortly after arriving in Bermuda he was taken with a chill, followed by a fever which lasted for a day or two. He had great thirst and drank large quantities of water. At this time he had massage each day for three or four days and the urine rapidly increased to 3,000 cubic centimeters in twenty-four hours. He was on a light diet with large quantities of fruit, especially oranges. From Bermuda he went to Nassau, where the temperature was higher and where he was able to take more exercise and felt much better. The urine ranged from 1,500 to 1,800 cubic centimeters daily. Early in March the patient returned to Pennsylvania, much improved in every way, the edema less marked, his strength greatly improved and with but little dyspnea on exertion. When the patient was seen June 10, 1908, there was but slight edema, traces being found in the neck, forearms, calves and about the ankles; this, as previously, seemed to be muscular rather than subcutaneous. The edema appeared to be more or less transitory. Sleeping in the sitting posture increased the edema of the legs, while sleeping in the recumbent posture increased it in the face, neck and arms. Exercise rapidly lessened the edema. The general health was good and the appetite was normal. Since the middle of February the patient has taken no medicine, except one ounce of Rochelle salts every other day and an occasional eight-grain blue mass pill. The cough has entirely ceased, except on severe exertion, and when it does occur it is without the previous spasmodic character. The patient has resumed part of his duties.

Examination of the Urine (H. C. Jackson).

As stated in the clinical notes, a preliminary examination of a twenty-four-hour specimen of the urine of November 21, 1907, showed a small volume of 340 cubic centimeters with a normal specific gravity of 1025. Qualitative tests indicated that no pathologic substances were present. The first indication of an abnormality was shown on testing for chlorids by the addition of silver nitrate to the urine made acid with nitric acid. The slightest precipitate, amountng to only an opalescence, resulted, indicating a practical absence of chlorids. At this time the patient was living on an ordinary hospital diet. Orders were immediately given for the preparation of a special diet which was as nearly free from salts, especially sodium chlorid, as could be obtained. Fluids were given in as large quantities as possible. The regular examination and analysis of twenty-four-hour samples of urine began on November 24, 1907, and continued until February 1, 1908, in all ten weeks. The analysis consisted in the determination of the volume, specific gravity, total nitrogen according to Kjeldahl's method, chlorids by Volhard's indirect method, phosphates by titration with uranium nitrate and the depression of the freezing point Δ by means of the ordinary Beckmann apparatus. At various times during the period of observation the ammonia and uric acid were estimated and were found to be normal in amount and in percentage of total nitrogen. At no time could albumin or casts be detected. The whole time of observation has been divided into four periods of from ten to

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thirteen days each. The first represents the time during the change from the normal to salt-free diet and includes nine days on the latter diet. The second follows the first, after a lapse of three days, and consists of the days just before, during and after the administration of potassium nitrate during a salt-free diet. The third, with three days' interval, represents the effect of the artificial Nauheim baths on the patient, who was still on the same diet. The fourth and last period begins after a lapse of eleven days, during which time the condition of the patient was steadily improving on the salt-free diet and continues during the period when an approximately normal diet was resumed. The patient, during the period of forced restraint from salt, developed a decided dislike to the condiment and it was only with considerable difficulty, by persuasion and by placing the salt in the food during preparation, that he was induced to take a definite amount (five grams) each day during the final period of normal diet. The tables for the four periods follow, with the discussion of the important points brought out in each:

Period I.

Previous to November 24, 1907, the daily volume of the urine averaged from 150 to 300 cubic centimeters and the administration of digitalis and potassium acetate and digitalin had little effect as regards the volume of output. It will be seen in the clinical report that the administration of water on the salt-free diet benefited this condition somewhat, as the volume rose at times to almost the normal with the specific gravity only a little below the average. The absolute chlorid elimination averaged almost two grams on the normal diet. This amount fell gradually during the salt privation, although at times it reached nearly to the normal diet figures for this individual. It is interesting to note that the chlorid percentage output did not vary with the absolute output of chlorin or with the elimination of water, but with some few exceptional days remained between 0.16 and 0.32 per cent. (see also the first two days in Table 2). This fact seemed to indicate that during the period of hydremic plethora following the ingestion of larger quantities of water the blood was able quickly to resume its then normal osmotic concentration by drawing from the salt of the tissues, and that the filtrate passing through the glomerulus was constant in composition and was normally concentrated in the convoluted tubules. On the other hand, the depression of the freezing point runs parallel with the specific gravity and inversely as the volume and in no relation to the chlorid output, absolute or percentage. Evidently, then, the nitrogenous constituents (urea, uric acid, kreatinin, etc.) were being eliminated in normal manner and variations in their output and percentage relations were causing the ordinary changes in specific gravity and depression of the freezing point. Neglecting the abnormally low chlorid elimination, and hence low specific gravity in relation to the volume of urine excreted, the other physical factors reacted perfectly normally. Thus no evidence could be obtained in any way, at any stage of the investigation, that the renal function was affected in the slightest degree. The phosphoric acid elimination was somewhat below the average, but,

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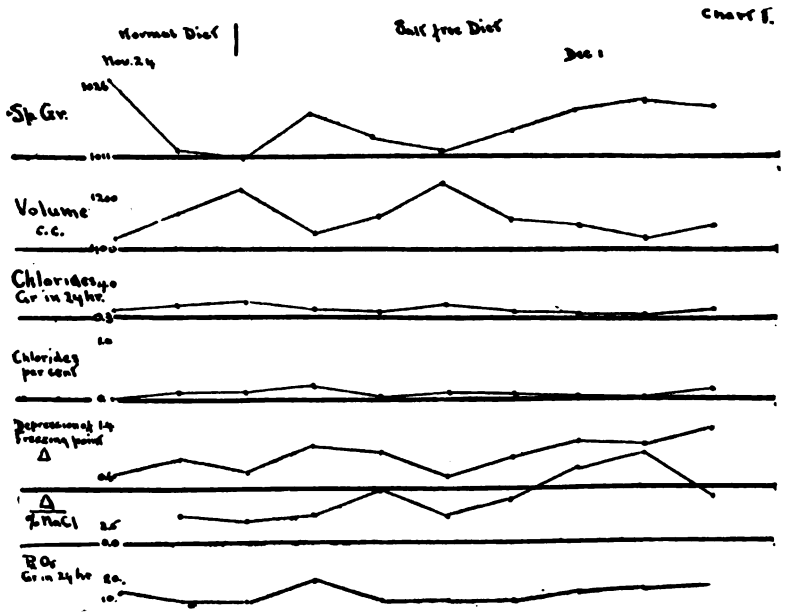
TABLE 1.

Date	Vol. cc.	Sp. Gr. 1.0—	Chlorids		P_2O_5 Grams	Δ	$\frac{\Delta}{NaCl}$	
			Grams	Per Cent.				
11/24	415	27	1.34	0.32	1.42	....	....	Normal diet.
11/25	800	13	1.92	0.21	1.07	0.87	4.1	Normal diet.
11/26	1150	11	2.53	0.22	1.10	0.665	3.2	Salt-free diet.
11/27	515	20	1.43	0.27	1.81	1.085	4.0	Salt-free diet.
11/28	700	15	0.84	0.12	1.14	0.950	7.9	Salt-free diet.
11/29	1220	12	1.95	0.16	1.16	0.545	3.4	Salt-free diet.
11/30	650	16	0.91	0.14	1.21	0.865	6.1	Salt-free diet.
12/1	535	20	0.53	0.10	1.47	1.100	11.0	Salt-free diet.
12/2	...	..	....	....	....	.....	....	
12/3	365	22	0.29	0.08	0.66	1.090	13.6	Salt-free diet.
12/4	540	21	1.08	0.20	1.49	1.280	6.4	Salt-free diet.

CHART OF TABLE 1.



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when considered in connection with the diet and amount of nitrogen excreted, it was considerably above the normal. We believe that the high $\frac{\Delta}{NaCl}$ factor was without value as an indication of any disturbed circulatory, cardiac or renal lesion (Korányi[1]), since this factor paralleled almost exactly the concentration of the urine as indicated by the specific gravity and depression of the freezing point.

Period II.

On December 9, 1907, the administration of potassium nitrate in doses of fifteen grains every three hours was begun and continued for three days followed after one day's intermission by a second period of three days with similar treatment. During all this time the salt privation was continued. The nitrate was selected[2] since, according to Sollmann, sodium nitrate stands as one of the few diuretics which occasions an increased percentage output of sodium chlorid coincident to the diuresis. The explanation offered by Sollmann is that the nitrate replaces the sodium chlorid in the tissues, thus throwing the latter substance out of combination and allowing of its excretion. In view of the relatively small amounts of potassium nitrate administered and the tremendous elimination of sodium chlorid which it caused, such an explanation seems hardly probable or even possible. As the table indicates, the potassium nitrate during the first period of ingestion caused a diuresis during which the volume increased to 3,225 cubic centimeters on the last day; the specific gravity was not markedly lowered owing to the fact that the percentage output of sodium chlorid was doubled; on the last day the absolute excretion of chlorids reached seventeen and four-tenths grams. The Δ remained unchanged; the increased concentration of the chlorids being counterbalanced by the decreased percentage elimination of the other soluble constituents of the urine, as is normally the case during diuresis. This again supports the view that the increased percentage output of chlorids is due to an increased ionic concentration of the blood in terms of this ion. The factor $\frac{\Delta}{NaCl}$ was reduced to the normal figures during this and the subsequent potassium nitrate period. The phosphoric acid output was somewhat increased in absolute amount, but the percentage figures were lowered during the diuresis. The second period of potassium nitrate ingestion differed slightly from the former in that the diuresis was not very evident; the increased chlorid output was quite pronounced, although not so marked as in the first period. This condition caused the Δ to increase and percentage of chlorid elimination to rise on one day

[1] v. Korányi, A.: Physiologische und klinische Untersuchungen uber den osmotischen Druck thierischen Flüssigkeiten *Ztschr. f. klin. Med.*, 1897, xxxiii, i; 1898, xxxiv, i.

[2] This substance was employed following the work of Sollmann (The Effect of Diuretics, Nephritic Poisons and Other Agencies on the Chlorids of the Urine, *Am. Jour. Physiol.*, 1903, ix, 423), who showed the diuretic effect of sodium nitrate and its power to increase both the absolute and percentage elimination of chlorids. The potassium salt was chosen in the hope that the well-known effect of these salts in replacing sodium compounds in the body (Bunge) might aid in producing a favorable result.

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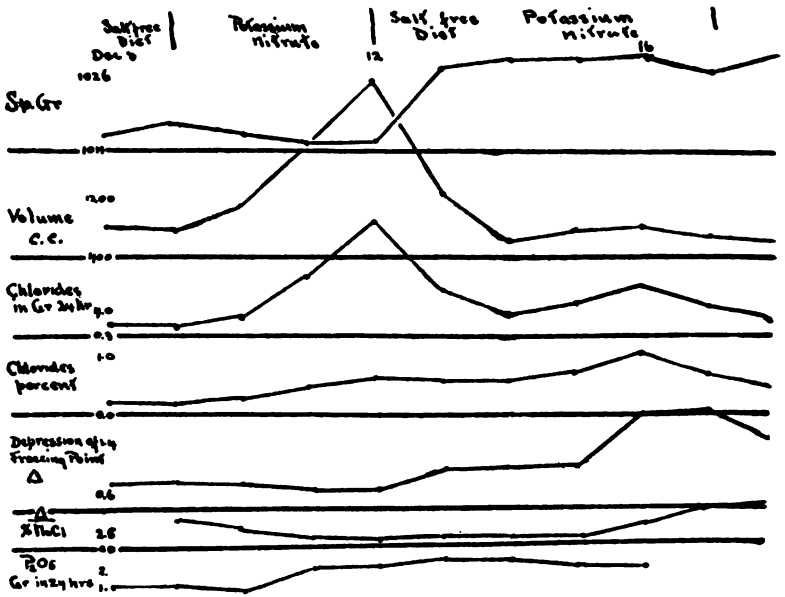
TABLE 2.

Date	Vol. cc.	Sp. Gr. 1.0—	Chlorids		P_2O_5 Grams	Δ	Δ / NaCl	
			Grams	Per Cent.				
12 /8	850	14	2.04	0.24	1.51	....	....	Salt-free diet.
12 /9	785	16	1.41	0.18	1.48	0.800	4.4	Salt-free diet.
12/10	1140	14	2.74	0.24	1.28	0.740	3.08	Pot. nitrate.
12/11	2110	12	8.86	0.42	2.00	0.650	1.50	Pot. nitrate.
12/12	3225	12	17.40	0.54	2.13	0.660	1.22	Pot. nitrate.
12/13	1300	26	6.50	0.50	2.08	0.775	1.55	Salt-free diet.
12/14	580	30	2.72	0.47	2.24	.....	....	Pot. nitrate.
12/15	700	28	4.06	0.58	3.42	0.875	1.50	Pot. nitrate.
12/16	790	30	6.95	0.88	2.27	1.765	2.00	Pot. nitrate.
12/17	610	24	3.42	0.56	1.98	1.845	3.33	Salt-free diet.
12/18	525	28	2.10	0.40	....	1.335	5.45	Salt-free diet.
12/19	615	20	1.48	0.24	....	1.470	6.12	Salt-free diet.

CHART OF TABLE 2.



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to almost normal figures. During the six days of drug administration and the two single days following each period, fifty-two and sixty-five hundredths grams of sodium chlorid were excreted, and this during a salt-free diet.

If we consider the weight of the patient at seventy-five kilos and deduct therefrom the proportional fraction of this due to bone, by a simple calculation one can determine that the presence of these fifty-two and six-tenths grams of sodium chlorid in the body before its elimination would have been sufficient to increase the osmotic concentration of the fluids of the whole body equivalent to that of about a one per cent. sodium chlorid solution. This will serve to indicate the extreme state of hypertonicity which must have existed in the fluids of the body before the administration of the potassium nitrate and to which it is believed the edema was due.

This period of somewhat incomplete analytical results covers the time of gradual recovery with continued salt privation. During part of this time, beginning on December 27, 1907, the patient was given a series of artificial Nauheim baths on alternate days, with the intention of stimulating the peripheral circulation. All previous attempts to cause sweating by hot baths, etc., had been fruitless. While the results are hard to explain, they are too evident to admit of doubt as to cause and effect. No change in the volume of urine was noticed, but the increased elimination of chlorids brought the percentage output almost up to normal on December 30 and to one and seven-tenths per cent. on December 28. During the period between January 1 and 12 the effect of abstinence from sodium chlorid became evident in the extreme lowness of the absolute output, amounting on the average to only forty-five one hundredths gram. This can be seen on examination of the first three days, Table 4.

Period IV.

This table details the results of the commencement and continuance of a somewhat normal diet in which sodium chlorid was not excluded, but during part of which sodium chlorid was administered in five-gram amounts *per diem*. The first ten days in the table are continuous; then follows a lapse of four days, and a subsequent period of three days is added in order to show the effect of the normal diet two weeks after its commencement. Finally, there follows the results of a partial examination of the urine of the same individual on May 19, 1908, or three and one-half months subsequent to the time when the patient left the hospital (February 1, 1908).

The figures for this period indicate that, while the volume of the urine had not assumed normal figures, the specific gravity was much higher with the same volume than was the case before the treatment began (Table 1). As striking evidence in favor of the view that the edema was set up by chlorid retention, there must be pointed out the tenacity with which the body has retained the chlorids in spite of deprivation of these salts; thus, after about seven weeks of salt-free diet, the body, even at that time, was not in a state of chlorid hunger, since the addition

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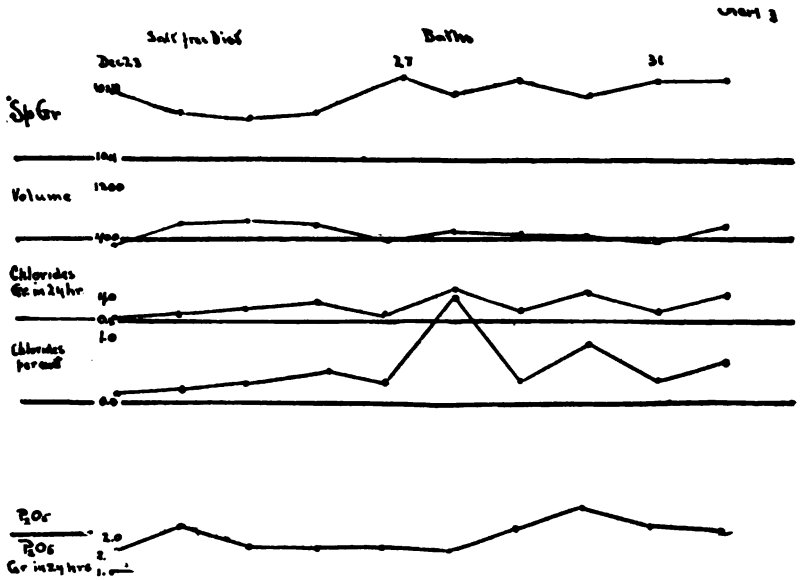
of five grams of salt to the diet caused the elimination, after three days, of over this amount and within the week following the body was almost in exact sodium chlorid equilibrium.

TABLE 3.

Date	Vol. cc.	Sp. Gr. 1.0	Chlorids		P_2O_5 Grams	
			Grams	Per Cent.		
12/23	347	25	0.5	0.14	1.37	Salt-free diet.
12/24	645	20	1.2	0.19	2.16	Salt-free diet.
12/25	705	19	2.1	0.30	1.37	Salt-free diet.
12/26	615	20	3.0	0.48	1.30	Salt-free diet.
12/27	400	27	1.2	0.30	1.25	Salt-free diet.
12/28	525	21	8.82	1.70	1.00	Salt-free diet + Nauheim bath.
12/29	475	26	1.5	0.31	1.59	Salt-free diet.
1 /30	480	23	4.2	0.88	2.19	Salt-free diet + Nauheim bath.
12/31	390	26	1.4	0.35	1.40	Salt-free diet.
	610	26	3.7	0.60	1.16	Salt-free diet + Nauheim bath.

CHART OF TABLE 3.



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That the absolute and percentage output of sodium chlorid have not reached the normal figures is to be attributed to the fact mentioned above, that the patient, on being allowed to resume a normal diet, complained that salt nauseated him and refused to eat foods which tasted at all salty. The Δ and the factor $\frac{\Delta}{NaCl}$ rapidly assumed normal figures after the establishment of the normal diet and have remained so ever since. The phosphoric acid elimination is now well within normal limits.

On the whole, the examination of the urine the day before the patient left the hospital and three and one-half months after shows it to be practically normal when the character of the diet is taken into consideration.

DISCUSSION.

It seems evident that the appearance of the edema noticed in this case was accompanied by a diminished elimination of chlorids; whether this was the result of the edema or its cause is difficult to prove, especially on account of the fact that it was impossible to obtain any of the patient's blood for examination and comparison with the urinary findings. In particular cases of edema associated with certain renal lesions the cause is ordinarily attributed to a deficient eliminating power of the kidney for chlorids. At no time before or during the progress of the disease did any evidence of renal deficiency exist. Apparently, with an increased concentration of the blood for chlorids, there followed an augmented output of these ions. It seems reasonable therefore that the discussion of the renal function in this connection may be excluded.

It is impossible at this time to enter into a complete exposition of the various theories which have been advanced to explain salt retention in relation to hydrops. The subject and its literature have been well covered by Georgopulos[3] and by Christian.[4] The principal contention rests on the question whether the salt retention is the cause or the result of the appearance of the hydrops. Strauss,[5] Widal,[6] Halpern[7] and Castaigne,[8] among others,

[3] Georgopulos: Experimentelle Beiträge zur Frage Nierenwasserucht, *Ztschr. f. klin Med.*, 1906, lx, 411.

[4] Christian, H. A.: Experimental Nephritis, *Boston Med. and Surg. Jour.*, 1908, clviii, 416, 452.

[5] Strauss: Therap. d. Gegenwart, 1902, iv, 444; 1903, v, 193.

[6] Widal: La cure de déchlorination, *Bull. Méd. des Hôp.*, Paris, 1903, xx, 773, 990.

[7] Halpern: Beiträge zur Frage des Verhaltens der Chlorid im Körper, ihre Beziehung zur Oedembildung und ihre Bedeutung fur die Diatetik bei Nephritis. Beitr. z. wissensch. *Med. u. Chem.* (Festschr. f. Salkowski), Berlin, 1904.

[8] Castaigne: Le rôle du reins dans la rétention cholorurée, *Semaine Méd.*, 1903, xxiii, 309; 1905, xxv, 472.

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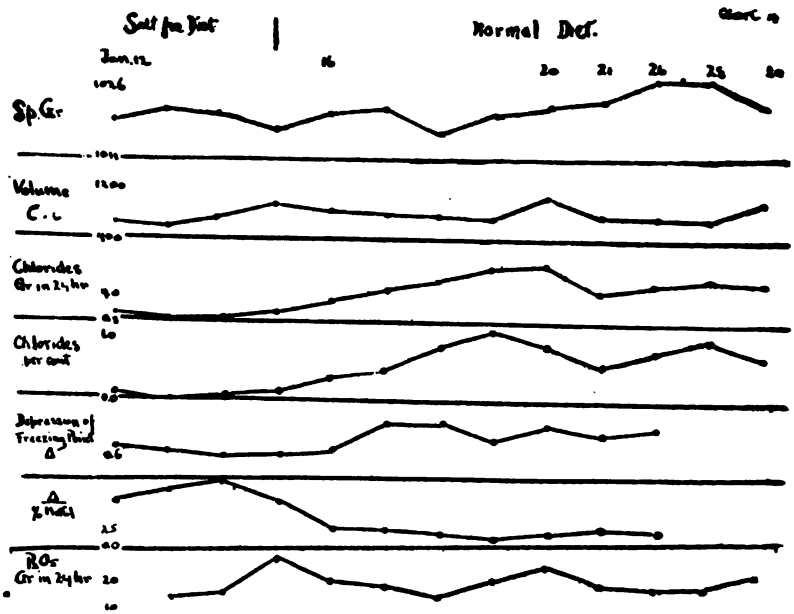
TABLE 4.

Date	Vol. c.c.	Sp. Gr. 1.10–	Chlorids		P_2O_5 Grams	Δ	Δ / NaCl	
			Grams	Per Cent				
1/12	665	18	1.10	0.16	....	1.135	7.08	Salt-free diet.
1/13	605	20	0.38	0.06	1.47	.....	.....	Salt-free diet.
1/14	710	19	0.48	0.09	1.64	0.975	10.80	Salt-free diet.
1/15	935	16	1.30	0.14	2.72	0.990	7.07	Normal diet.
1/16	805	19	2.86	0.35	2.09	1.080	3.08	Normal diet.
1/17	755	20	4.23	0.56	1.86	1.480	2.65	Normal diet.
1/18	715	15	5.58	0.78	1.47	1.450	1.86	Normal diet + 5 grams NaCl.
1/19	675	19	7.31	1.09	....	1.200	1.10	Normal diet + 5 grams NaCl.
1/20	975	22	7.60	0.78	2.42	1.400	1.80	Normal diet + 5 grams NaCl.
1/21	695	23	3.75	0.54	1.79	1.250	2.34	Normal diet + 5 grams NaCl.
....	.....	..	....	....	....	.....	.....	
1/26	665	26	4.67	0.70	1.65	1.345	1.92	Normal diet + 5 grams NaCl.
1/28	660	26	5.54	0.84	1.67	.....	.....	Normal diet + 5 grams NaCl.
1/30	890	21	5.01	0.56	2.22	.....	.....	Normal diet + 5 grams NaCl.
....	...	..	....	....	....	.....	.....	
19/5	1170	15	7.76	0.66	2.45	.....	.....	Normal diet.

CHART OF TABLE 4.



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believe that the salt retention in the tissues is primary to the retention of water; the latter observer bases his views on experiments in which saline was injected into normal animals and those with experimental nephritis. The urine in both cases showed no difference. But if sound and diseased animals were bled and saline injected very soon afterwards, the blood of the nephritics contained less salt. The fact that in certain febrile conditions there exists a retention of chlorids without evident renal disturbance is also cited as evidence of the primary nature of the retention. In these cases edema does not necessarily result; and this seems sufficient reason to believe that the factor of permeability of the epithelial lining of the capillaries forms a not unimportant adjunct to the whole process. Müller[9] advances this view and considers that the hydrops is due to an increased permeability of the blood vessels due to certain toxic products in the blood. This conception receives support from Cohnheim and Lichtheim,[10] who showed that subcutaneous edema only followed saline injection when the skin had been irritated in any way, and the results of Magnus with chloroform irritation pointed in the same direction.

In view of the extremely obscure etiology of the case under discussion it would seem to us that a combination of Müller's explanation and that of increased combining power of tissues for chlorids must form the basis for any reasonable explanation of the condition. Nothing in the history of the case points to any anatomic lesion which might account for the hydrops. The appearance in the blood of toxic products inhaled through the lungs as the result of continued sojourn in the vitiated air of a chemical laboratory might readily set up changes in the epithelial lining of the capillaries rendering them more permeable and at the same time bring about changes in the protoplasm of the cell by which the combining power of the proteins would be increased. This in turn would cause an increased osmotic concentration in the cells and as an attempt to reduce this, water would be drawn from the blood. This view would explain, on the one hand, the failure of digitalis and similar agents to cause a diuresis, the dryness of the skin and inability to produce sweating in hot baths; and, on the other hand, the beneficial effects of artificial Nauheim baths in stimulating the cutaneous circulation and capillary epi-

[9] Müller Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 64.

[10] Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, *Virchow's Arch. f. path. Anat.*, 1877, lxix, 106.

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thelium, and the effect of potassium nitrate in starting the replacement of the combined chlorids by means of the nitrate, after which the reduction in ionic concentration, followed by means of mass action. Bunge[11] might be more prone to explain this last process as a replacement of the sodium ion by potassium.

Finally, it must be mentioned that Georgopulos and others present strong arguments against the view that the water retention is secondary to the salt retention. They believe that the kidney becomes more impermeable to water, a hydremic plethora results and the tissues become overladen with water as a result. Georgopulos states with truth that an increase in the salt content of the tissues during the so-called salt retention has never been proved by experiment. This, however, may have been due to faulty methods. At present it is impossible to decide these disputed points. Nevertheless, we feel inclined to believe, from all the evidence which we have been able to obtain from the results derived from the study and treatment of the case, that the above explanation is possible and most probable and that we are dealing with a case of chlorid retention brought about by the action of some general toxemia which occasioned an increased permeability of the capillaries to chlorids and an augmented combining power of the protoplasm for these ions.

OCCURRENCE OF SPONTANEOUS ARTERIAL DEGENERATION IN THE RABBIT.*

By RICHARD M. PEARCE, M. D.

As one of the earlier investigators of lesions of the vascular system occurring in the rabbit after intravenous injections of adrenalin[1] I have been interested in the observation of Drs. Miles and Johnstone[2] concerning the frequent occurrence of spontaneous arterial lesions. These investigators suggest that the vascular lesions, ascribed by many observers to the injection of adrenalin, are in reality of spontaneous origin. In support of this view they present the results of the examination of a large num-

[11] Bunge: Lehrbuch der physiologischen Chemie, Leipsic, 1900.

* Work done under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Am. Med. Assoc.*, 1908, li, 1056.

[1] *Jour. Exper. Med.*, 1906, viii, 74, 400; *Am. Jour. Med. Sciences*, 1906, cxxxii, 737.

[2] *The Journal A. M. A.*, Oct. 5, 1907.

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ber of normal rabbits in which lesions similar to those produced by adrenalin occurred with equal or greater frequency.

The inevitable conclusion is either that the spontaneous lesions are common and that the individuals working with adrenalin have been careless about their controls, or that rabbits of certain localities, or those raised or kept under certain conditions, are peculiarly prone to spontaneous lesions. The first of these conclusions has been met by Dr. Joseph L. Miller,[8] who points out that in Jores exhaustive review of the many attempts, often on a large scale, to produce arteriosclerosis experimentally there is no mention of successful results. These experiments included the use of a variety of substances and in by far the larger number the rabbit was used. Furthermore, during the past few years many attempts have been made to produce arterial lesions by subcutaneous and intraperitoneal injections of adrenalin as controls of the intravenous administration; a procedure necessitating a very careful comparative study of the rabbit's vascular system.

The only spontaneous lesions, according to Miller, which were described previous to the work of Miles and Johnstone were the slight changes described by Fisher in poorly nourished animals, a single instance reported by Ophüls and possibly the atheroma, in two rabbits, ascribed by Croftan to injections of hypoxanthin. Miller, moreover, points out that in Loeb's series of 100 normal rabbits and Meronescu's of 300, no lesions were found and also that the subcutaneous adrenalin injection experiments of Miles and Johnstone are of no value. The weight of evidence, therefore, does not support the suggestion that spontaneous lesions are general but have been overlooked by the neglect of control observations.

In this respect, however, I must admit my negligence in not reporting control observations in my earlier communication. Control observations were made on a small number of animals with entirely negative results, but on account of the small number were not published. During the past winter, in order to determine the incidence of spontaneous lesions in the rabbits supplied to the Bender Laboratory, I have examined sixty-two animals. Except for six pairs obtained from dealers in Pittsfield and Brookline, Mass., these animals were procured in the neighborhood of Albany, usually in small lots of one, two or three pairs, and in large

[8] *The Journal A. M. A.*, 1907, xlix, 1789.

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part were animals which had been caught in the fall and domesticated but a short time. Of these, fifty-one may be considered presumably normal animals in that they had not been used previously for experiment of any kind, or were used only on the day of killing for blood pressure experiments or to obtain blood or fresh organs. They also represent animals which, in that they were used shortly after purchase, did not pass through a long laboratory life. They may be grouped roughly according to size into three groups of about equal number as large, small, and medium size. Vascular lesions were found in but three; these consisted, in each, of a few minute patches at the beginning of the aorta. All were large animals and presumably full grown.

Of the remaining eleven animals, one suffered from an abscess of the hip; three had received repeated injections of dog's serum; one, nephrotoxic serum; one, human blood; one, typhoid bacillus and three, chrome salts. These were all in the laboratory for several weeks or months. In this group lesions of the aorta occurred in four; in the animals receiving, respectively, injections of typhoid bacillus, dog serum, nephrotoxic serum and human blood. In two of these the lesions were diffuse involving irregularly the entire aorta and comparable to those produced by adrenalin. In the other pair a few small areas were present at the beginning of the aorta only.

This control study shows that spontaneous lesions were found in three of fifty-one presumably normal rabbits or in practically six per cent., or, if the animals used for various experimental purposes are included, in seven of sixty-two animals or eleven per cent. This last view, however, is hardly fair, for as the lesions were present in four animals of the second group, or in thirty-six per cent., it cannot be denied that the experimental procedure may possibly have had some share in their production. Certainly the influence of typhoid toxin and alien sera can not be entirely set aside in view of our knowledge of the very general degenerative changes which these substances cause.

In this connection it may be mentioned that Israel[4] in his study of the relation of heart hypertrophy to experimental nephritis has described and pictured a very diffuse lesion of the aorta in a rabbit receiving injections of alcohol directly into the kidney. This observation has been quite generally ignored in the recent

[4] *Virchow's Archiv.*, 1881, lxxxvi, 299.

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literature of experimental arteriosclerosis; but Israel's illustration plainly pictures a lesion of the aorta not to be distinguished from that caused by adrenalin.

It would appear, therefore, that while spontaneous arterial degeneration may occur in the rabbit, it is not as constant a condition in all localities as the investigations of Miles and Johnstone indicate. Moreover, the figures here presented offer a satisfactory control of my earlier report on the general subject of experimental arteriosclerosis due to adrenalin and the later report in which I conclude that single doses of adrenalin may cause arterial lesions, a conclusion which might appear doubtful if viewed only in the light of the experiments of Miles and Johnstone.

In my opinion the occurrence of spontaneous lesions in the rabbit does not diminish the importance of the lesions due to adrenalin, but on the contrary, increases their importance, as an example of a lesion occasionally occurring naturally, but which may readily be produced experimentally. The rabbit thus becomes a peculiarly valuable animal for the study of vascular lesions, for the interest of the adrenalin lesion lies not so much in its arteriosclerosis-like nature as in the opportunity offered for the study of degenerative and reparative lesions of arteries.

The possibility of a variety of factors operating to cause vascular injury is suggested by the four positive findings in the second group of eleven rabbits. The contrast with the first group is very striking and would indicate that a study of the arterial system of a large number of rabbits, kept under a variety of conditions, and subjected to various experimental procedures, would yield results of great value concerning chronic vascular lesions.

Finally it may be stated that the demonstration of these spontaneous lesions in no way vitiates the importance of the experimental lesions but does demand a very careful control study of the rabbits in each locality in which experiments are made.

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THE EFFECT OF CONDITIONS UPON THE LATENT PERIOD AND RATE OF ASEPTIC POST-MORTEM AUTOLYSIS DURING THE FIRST TEN HOURS.[1]

By HOLMES C. JACKSON.

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The experiments about to be described had for their purpose an attempt to determine the character of the initial physical or chemical changes which occur in an organ as the result of its becoming disconnected from the blood supply, and are responsible for the setting up anew or the gaining ascendancy of those catalytic processes commonly known as autolysis. It seemed that information gained in this direction would be of especial value in a discussion of the question as to whether autolytic processes present but a survival of the same or similar processes occurring in the living cell or whether they represent reactions set up *de novo* as the result of incipient somatic death.

The point of attack in such a problem must fall upon the initial or early hours of the autolytic process. On this account, one may neglect in the discussion the almost numberless investigations dealing with autolytic processes in general and the effect upon them of changes in condition such as reaction, etc., and confine oneself to the experiments in which the autolysis was studied with especial reference to the first six to eight hours after shutting off the circulation from the organ either by removal from the body or otherwise.

But few investigators have busied themselves directly with this line of work. Of first importance must be considered the work of Lane-Claypon and Schryver (1) which indicates that the course of autolysis in the first twenty-four hours may be divided into three stages; (*a*) a latent period of from two to four hours, (*b*) a period of rapid autolysis and (*c*) a period of gradual autolysis.

Of perhaps chief interest in this connection is the latent period of two to four hours existing between the removal of the tissue from the body and the commencement of autolysis. If such a

[1] Conducted under a grant from the Rockefeller Institute for Medical Research. Read by title before the American Society of Biological Chemists, Chicago, Ill., January 2, 1908. Abstract appeared in the *Journal of Biological Chemistry*, 1908, 4, Nos. 4 and 5, p. xxxvii Received for publication October 12, 1908.

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latency in autolysis does exist and is not the result of some condition of the experiment, then it becomes natural to conclude that this latent period represents the time during which the condition of the cell is being so changed by the lack of circulating blood and perhaps other causes that new or more rapid catalytic reactions may take place and set up a disintegration more pronounced than occurs during cellular life. Such reactions may be originated in various ways. Lane-Claypon and Schryver found that the state of nutrition markedly influenced the course of the autolysis in that the latent period was absent in the livers of fasting animals and that these tissues underwent more rapid decomposition than was the case in the well-fed animal. This is explained with the assumption that since it is probable that enzymes are liberated in the process of autolysis, the fasting liver contains more enzymes free to act (uncombined) or in the form of corresponding zymogen. The latent period is taken as indicating that in the well-fed animal a preponderance of the enzymes are in the form of zymogens and that the first stage in autolysis consists in the transformation of zymogen into active zymin. The presence of free enzymes in fasting animals indicates to these authors the probability that the liberation of these enzymes acts as a normal mechanism for the *intravitam* utilization of proteins in tissues—the supplying of food when none is taken in per os.

In a subsequent paper (2) Schryver has somewhat altered his theory of enzyme liberation as a cause of the latent period in order to correspond to criticisms of Wiener (3), who claimed that the latent period was merely due to the natural inhibitory effect of the alkaline reaction of the living tissues and that the latency ended with the sufficient neutralization of the alkalies by means of the acids formed in autolysis. This, of course, is reasoning in a circle since it does not explain what originates or accelerates the process by which the acids are formed for neutralization purposes.

Schryver has advanced a somewhat complicated theory for the preservation of chemical equilibrium in the living cell. The equilibrium of enzymes is established by the presence of an excess of ammonia which prohibits the formation of an acid reaction, necessary for autolysis. During starvation, the excess of ammonia gradually disappears and when the production of acid is sufficient to supersaturate the alkalinity, the autolytic

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enzymes liberate aminoacids; these in turn are transformed in the liver with the production of ammonia which again inhibits the autolytic processes. The non-nitrogenous moiety of the autolytic products serves as food for the fasting cells.

It can hardly be conceived that the author believes that free ammonia is present in the cell at any time, although this is necessary to the theory. In view of the neutrality of protoplasm and the extreme variations which may occur in the production of acid and of alkali without change in this neutrality as shown by Henderson and Black (4), Schryver's position seems untenable.

On account of the many possible explanations for the latent period and its importance in deciding the cause of autolysis, it seemed of sufficient interest to examine this subject somewhat more closely and to attempt if possible to shorten or prolong the period by altering the conditions of the experiment.

In order to obtain an insight into the character and velocity of the reactions taking place in the liver after its removal from the body, three factors were determined during the autolyses.

1. The changes in the depression of the freezing point. This method has been employed by several authors and more recently by Fredericqs (5), Delrez (6) and by Wells and Benson (7). The first of these investigators employed a somewhat complicated procedure in the preparation of the tissue for examination. The methods seem faulty and have been criticized by Wells. The latter two authors have determined coincidently the changes in the electrical conductivity and depression of the freezing point during autolysis. Both authors report that in general these factors parallel each other closely. In this work therefore the determination of the electrical conductivity has for various reasons been neglected.

2. The increase or decrease in noncoagulable nitrogen.

3. Changes in reaction were examined by means of phenolphthalein and dimethylaminoazobenzene. Body fluids react acid to the former and alkaline to the latter; phenolphthalein is particularly sensitive to changes in the hydrogen ionic content while dimethylaminoazobenzene only indicates an H^+ concentration about equal to that of an 0.8 per cent. lactic acid solution. In this way it seemed possible to determine the character of the substances causing the change in reaction, if such occurred.

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The general method of experimentation was as follows: The liver tissue was removed aseptically,[2] passed through a sterile hashing machine into a sterile Erlenmeyer flask of 500 cubic centimeters capacity provided with a cotton plug. The flask containing 300 cubic centimeters of the salt solution (cold or at 38° C.) in which the autolysis was to proceed was counterpoised on scales and 100 grams of the ground tissue were weighed out by allowing the material to drop from the machine directly into the flask. During the process the whole apparatus was covered with a sterile cloth to exclude air contamination. The mixture being thoroughly shaken a control sample of 50 cubic centimeters was removed with bacteriological technique into a smaller stoppered flask. This was brought to the boiling point without change in reaction, allowed to cool, thoroughly mixed, and filtered.

This coagulum-filtrate was immediately put through the routine examination for determination of the depression of the freezing point by means of Beckmann's apparatus,[3] determination of the noncoagulable nitrogen by the Kjeldahl method and titration of the respective acidity by means of phenolphthalein and alkalinity to dimethylaminoazobenzene. For each of these determinations ten cubic centimeters of the filtrate were employed and all were conducted in duplicate.

After the removal of the control sample the flask was placed in the thermostat at 38° C; when the liver was not irrigated this occurred about twenty minutes after the death of the animal; the washing of the organ occupied ten minutes longer time. At definite times as indicated by the protocols, samples of 50 cubic centimeters were removed with bacteriological technique, the sample coagulated as above and the main flask returned to the incubator. At each time when a sample was withdrawn, a drop of the autolytic mixture was allowed to fall upon a sterile agar slant and at the end of the experiment these were incubated at 38° C. for from twenty-four to forty-eight hours. In practically all cases where the experiments ran for only six to eight hours, the agar slants when examined by a stained smear gave negative results—indicating a practical absence of organisms or,

[2] The usual surgical operative technique was employed.

[3] Several control examinations were made as to the depression of the freezing point of the coagulated and uncoagulated samples. The two gave results which were almost identical or within the limit of accuracy of the work.

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at least, that they were in such small numbers that a drop of the mixture taken at random failed to include one of them. All experiments in which the slant or smear indicated organisms, have been excluded. In the experiments where the period was extended, it was noticed that at times at the twelfth hour there was evidence of the presence in small numbers of certain organisms. In some instances the tests would remain negative even at twenty-four hours; in others the hay bacillus or another bacillus which will be discussed in a short note by Jackson and Hawn, made its appearance between twelve and twenty-four hours in quantities sufficient to give decidedly sour nonputrefactive odor to the autolytic mixture. In this connection must be mentioned the work of Magnus-Levy (8) who showed that acids of fatty nature as well as methane and hydrogen sulphide are produced during the first twenty-four hours of aseptic liver autolysis. His results as regards acidity are confirmed in the work presented here. This author also experienced the same difficulty in obtaining sterile organs that was met with in this work. Experiments in which infection has occurred have either been omitted or a note of the infection made in the protocol. In some other experiments a decided putrefactive odor appearing between six and eight hours indicated contamination of some sort; no account has been taken of these.

Note must also be made of the fact mentioned by Schryver (9) and others that very frequently the glycogen when present in the liver of the dog disappeared very slowly during the autolysis. In certain experiments it was still present at the end of six hours of incubation; at times, however it would disappear earlier, but no instance can be found in the notes where the first or third hour sample was negative when the control indicated the presence of glycogen. Schryver states that in fasting dogs the glycogen disappears very quickly, while it remains for twenty-four hours in the livers of well-fed animals. It is hard to explain why livers of animals which have fasted for several days should contain glycogen at all, since it is ordinarily believed that in starvation it disappears quite quickly. In only some of the fasting animals in the experiments of this paper did glycogen appear in the liver; it is therefore manifestly impossible to make comparison with Schryver's results. The variations in appearance of glycogen and the rapidity of its disappearance noticed in the well-fed animals renders Schryver's distinction improbable however. The probable

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relationship of the slow disappearance of glycogen from the liver post-mortem and of its presence or absence to the autolytic processes going on, is discussed elsewhere in this paper.

Again in certain autolyses the mixture after the second or fourth hours began to take on a greenish nuance which developed quite rapidly in intensity until at the sixth hour, the color became dark green, almost black. This was noticed, of course, in a comparison of the coagulum-filtrates at the end of the experiments and seemed most prone to occur in those cases where the liver contained glycogen; the phenomenon remained present throughout the autolysis. Without doubt this peculiar condition was the result of the presence of oxidizing enzymes similar to tyrosinase and to those which noticed in plants by Palladin (10) and others, transform colorless into dark colored compounds, pigments or melanines.

As evidence of the accuracy of the experiments and the limits of error which the technique involved, reference must be made to the protocols of two experiments No. 25A, B and C and 26A, B and C.[4] In these cases three controls were simultaneously started the only difference being that two of them in each experiment were kept in the dark. Since this condition did not seem to effect the autolyses, the results serve as admirable controls of the method.

The experimental evidence obtained as the result of this work will be taken up as follows:

1. Effect on latent period of (*a*) condition of animal, (*b*) presence or absence of blood, (*c*) temperature of diluent salt solution.

2. Effect of conditions upon the commencement and rate of the autolysis. (*a*) nutritional state of the cell, (*b*) light, (*c*) antiseptics, (*d*) reaction, (*e*) salt concentration.

LATENT PERIOD.

Effect of Nutrition.—Schryver's experiments indicated that the best conditions for obtaining a latent period were present in the livers of well-fed animals. Hence Series I (four experiments) was carried out after the general method indicated previously in the paper. The animals were well-fed for several days previous to death; the livers were taken out without irrigation and *cold* physiological salt solution (Δ=0.568) added in appropriate amount. The whole mixture of tissue and salt solution was then

[4] See Tables II, III and IV.

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placed in the thermostat at 38° C. All experiments (5a, 5b, 6, 10) showed (Table I) that the depression of the freezing point

TABLE I.[5]

Series I

Liver Unwashed; Cold Saline Solution	Control	1 Hours	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours	7 Hours
Exp. 5a	0.670 6.20	0.655 5.20	0.665 5.25	0.680 5.05	0.690 5.35	0.715 5.95	0.750 6.60	
Well-fed	0.55 0.85	0.60 1.00	0.65 1.15	0.70 1.30	0.75 1.45	0.85 1.65	1.85 2.20	
Exp. 5b	0.670 —	— —	0.665 5.65	0.665 5.75	0.685 5.55	0.685 5.55	0.695 5.65	0.710 5.85
Well-fed	0.30 1.00	0.40 1.05	0.40 1.00	0.35 0.95	0.55 1.00	0.60 1.00	0.65 0.95	0.70 0.95
Exp. 6	0.665 7.00	0.650 6.15	0.660 5.90	0.655 6.60	0.665 7.80	0.665 8.00	0.675 8.30	0.690 —
Well-fed	0.50 1.20	0.50 1.10	0.50 1.15	0.60 0.95	0.65 0.90	0.80 0.95	0.85 0.95	0.90 1.00
Exp. 10	0.675 7.45	— —	0.660 6.85	0.660 7.35	0.675 7.60	0.685 7.85	0.720 7.60	0.725 7.70
Well-fed	0.75 1.35	— —	0.90 1.40	1.05 1.25	1.05 1.35	1.10 1.30	1.30 1.55	1.35 1.40

Series II

Exp. 14	0.600 7.35	0.595 7.45	0.605 7.70	0.615 7.75	0.615 7.85	0.620 7.90	0.645 8.45
Not fed	0.75 1.35	0.90 1.40	1.05 1.25	1.05 1.35	1.10 1.30	1.30 1.55	1.35 1.40
Exp. 22	0.660 6.95	0.685 7.20	0.710 7.10	0.700 6.90	— 7.20	0.710 7.20	0.715 7.10
Not fed	0.40 0.90	0.50 0.95	0.70 1.00	0.70 0.90	0.95 1.05	0.90 1.10	1.10 1.00
Exp. 28A	0.235 5.80	0.235 4.65	0.240 4.55	0.290 4.35	0.330 4.45	0.340 4.40	0.345 4.55
Not fed	0.40 1.35	0.55 1.15	0.45 1.25	0.60 1.20	0.85 1.25	1.05 1.10	1.35 1.35
Exp. 19	0.670 5.95	0.710 6.00	0.720 5.75	0.725 5.75	0.735 6.00	0.755 6.30	0.790 7.50
Well-fed	not done						

remained practically the same as the control with a slight tendency perhaps to decrease until the third or the fourth hour after which a more or less marked increase occurred to the end of the experiment. The figures for the non-coagulable nitrogen although somewhat fragmentary indicate also a positive decrease from the control occurring during the first three or four hours. The

[5] The upper left-hand figures represent degrees of depression of the freezing-point; the upper-right hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

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figures for the fifth and sixth hours rising above the control are indicative of the commencement of nitrogenous autolysis. The acidity to phenolphthalein increased without much evidence of latency except in Experiment 6 while the figures for the alkalinity to dimethylaminoazobenzene vary—two experiments showing no change, one an increase and one a decrease. The figures considered as a whole would certainly convey the impression that autolytic changes of the usual type had not begun to show themselves until between the third and fourth hour after removal of the tissue from the animal's circulation.

In the endeavor to control the statement of Schryver that the fasting livers did *not* show this latent period, Series II of three experiments (14, 22, 28A) were conducted in a manner similar in all details to Series I except that the animals were fasted for a few days previous to use. The livers were free from glycogen with the exception of that used in Experiment 28A.

In the protocol (Table I) the results for the depression of the freezing-point show that in two experiments a latent period of two hours existed while in the third (Experiment 22) autolysis began immediately. The figures for non-coagulable nitrogen in Experiments 22 and 28A however, point strongly to an inhibition of autolysis which lasted for five hours. In Experiment 28A the animal had not received food for three days previously; the liver contained glycogen which however gradually disappeared until no evidence of it could be obtained at the fourth hour, at which time it will be noticed that the marked depression of the freezing-point stopped. The non-coagulable nitrogen of the successive samples showed a marked diminution over the control with no evidence of an increase—rather a decrease—to the end of the experiment. This peculiar relation of glycogen disappearance to changes in the depression of the freezing-point and non-coagulable nitrogen will be taken up later in the paper. Finally one experiment (19) with a well-fed animal similar to those of Series I gave no latent period as indicated by the depression of the freezing-point but the non-coagulable nitrogen figures showed an inhibition of autolysis lasting until the fourth hour. In all of the experiments in Series II the acidity figures with phenolphthalein showed a consistent increase from the very beginning of the experiment, while the alkalinity to dimethylaminoazobenzene remained constant to the end.

Although Series I with well-fed animals resulted as expected

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according to Schryver, Series II with three fasting animals and one well-fed animal was unsatisfactory.

Turning about to find a cause for these varying results and at the same time attempting to obtain some condition which might influence the latency of the autolysis, it seemed plausible to try the effect of two factors; first, the absence of blood; and second the use of *warm* (38° C.) saline at the outset of the experiment.

Effect of Blood.—The elucidation of the question as to the effect of blood upon the latent period would bear directly upon the criticism of Schryver by Wiener mentioned above, as well as serve to accentuate the fact of the well-known inhibitory effect of blood upon the rapidity of autolysis noticed so frequently[6] although its cause is so poorly understood (11). The washing of the alkaline blood from the liver would tend certainly to remove a certain amount of bases from the organ together with other salts lost by diffusion during irrigation with the salt solution. Consequently two experiments (Series III) were conducted in which the livers were thoroughly irrigated through the portal vein with cold saline solution and diluted with cold saline solution; one animal was fasting (20) and the other well-fed (17). From the figures (Table II) for the depression of the freezing-point no latency of autolysis occurred and the increase is pronounced to the end of the experiment. The same is true for the non-coagulable nitrogen except that a slight indication of possible latency showed itself in the well-fed animal. The acidity to phenolphthalein increased and the alkalinity to dimethylaminoazobenzene remained constant as usual.

These two preliminary experiments seemed sufficient to make it evident that the presence of blood formed one of the inhibitory factors in the latency. This fact is of course not new except as it applies to the latent period and was to be expected since, as was stated above, the inhibitory effect of alkalies upon autolysis and their supposed action in prohibiting autolysis *in vivo* might be considered as persisting some time after removal of the organ after death.

Effect of Temperature of Salt Diluent.—The next series (IV) was planned to determine the effect of keeping the organ at body temperature during removal and subsequent autolysis. The washing was therefore accomplished with *warm* saline and *warm* saline added as diluent. The only time during which a lowering of tem-

[6] Schryver (p. 180), in one experiment, found no difference in the rate of autolysis between the perfused organ and one containing blood.

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TABLE II.[7]

Series III

Liver Washed; Cold Saline	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 20	0.555 5.40	0.570 5.90	0.590 5.80	0.595 6.10	0.600 6.30	0.610 6.40	0.625 6.60
Not fed	0.35 0.70	0.40 0.65	0.70 0.70	0.75 0.80	0.80 0.85	0.95 0.80	1.05 0.90
Exp. 17	0.565 5.05	0.585 4.95	0.600 5.15	0.620 5.50	0.640 5.65	0.650 5.80	0.710 6.30
Well-fed	0.50 1.00	0.60 0.90	0.70 0.95	0.80 0.95	0.85 1.20	1.00 1.15	1.10 1.05

Series IV.

Liver Washed and Diluted with Warm Saline							
Exp. 9	0.575 5.70	0.595 6.35	0.605 7.05	0.620 7.35	0.635 8.65	0.665 9.65	0.670 10.50
Well-fed	0.50 1.15	0.85 1.20	1.15 1.40	1.15 1.50	1.25 1.50	1.35 1.50	1.60 1.95
Exp. 11	0.555 5.40	0.540 5.35	0.585 5.50	0.590 5.70	0.590 6.15	0.615 6.30	0.640 6.80
Well-fed	0.50 1.10	0.65 1.25	0.80 1.05	0.80 0.95	0.9 1.00	1.00 1.25	1.10 1.35
Exp. 15	0.615 6.30	0.605 6.10	0.615 6.20	0.635 6.35	0.640 6.50	0.645 7.20	0.670 8.25
Well-fed	0.40 1.00	0.55 1.00	0.60 0.95	0.75 0.95	0.90 1.00	1.00 1.25	1.10 1.35
Exp. 18	0.660 5.30	0.675 5.85	0.705 5.90	0.710 6.30	0.725 6.70	0.735 6.80	0.740 7.25
Well-fed	0.40 0.60	0.60 0.95	0.65 0.95	0.70 0.75	0.85 0.75	0.90 0.65	1.05 0.75
Exp. 29E	0.325 4.50	0.345	0.365 5.70	0.385	0.395 6.45	0.415	0.435 7.45
Not fed	0.45 0.75	0.65 0.80	0.80 0.80	0.95 0.70	1.10 0.75	1.20 07.5	1.40 0.70
Exp. 26A	0.560 4.75	0.565 5.10	0.575 5.55	— 6.00	0.585 6.50	0.600 7.15	0.625 7.65
Not fed Dark	0.35 060.	0.50 0.70	0.75 0.65	0.80 0.60	0.85 0.70	0.90 0.75	1.00 0.80
Exp. 26C	0.555 4.90	0.565 4.95	0.570 5.25	0.585 6.30	0.610 6.75	0.620 7.00	0.625 7.45
Not fed	0.20 0.50	0.35 0.75	0.55 0.85	0.75 0.80	0.90 0.75	0.95 0.80	1.05 0.85

perature could occur was during the period of hashing. This, of course, represented only a few minutes and could cause at most a temperature depression of a few degrees. Some of the hashed material was tested and gave 34.5° C. The warm saline quickly brought this up to 37° C. Seven experiments were carried on in

[7] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower left-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

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this way (Experiment 9, 11, 15, 18, 29E, 26A, 26C). Of these the first four were well-fed and the last three fasting animals. Of the well-fed animals two (9, 18) showed (Table II) a marked autolysis at the outset as indicated by the figures for the depression of the freezing-point and nitrogen. On the other hand in Experiments 11 and 15 a well-marked latent period was present although it persisted for only one hour. Only traces of glycogen were present in the liver of Experiment II and it was absent in Experiment 15. The fasting animals whose livers were irrigated and diluted with warm saline gave figures both for depression of the freezing-point and nitrogen indicating no latency and an autolysis which was the most marked of all the experiments of this type.

A fifth series of four experiments (25A, 25C, 31C and 36A) were conducted with unwashed livers of well-fed animals employing warm saline as diluent. Three showed (Table III) immediate

TABLE III.[8]

Series V

Unwashed Liver Well-fed Warm Saline	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 25A	0.730	0.745	0.775	0.790	0.810	—	0.840
	5.10	5.40	5.60	5.70	5.80	—	6.30
	0.30	0.50	0.60	0.65	0.75	—	0.95
Dark	0.65	0.55	0.65	0.80	0.90	—	1.20
Exp. 25C	0.725	0.755	0.780	0.795	0.810	0.825	0.835
	4.65	4.90	4.95	5.10	5.20	5.65	5.85
	0.4	—	0.55	0.65	0.70	0.85	0.95
	0.50	0.60	0.70	0.85	0.90	1.05	1.10
Exp. 31C	0.530	0.590	0.605	0.625	0.645	0.660	—
	6.10	6.20	6.25	6.35	6.70	7.00	—
	0.50	0.60	0.70	0.75	0.85	0.85	0.95
	0.70	0.80	0.80	0.65	0.80	0.60	1.35
Exp. 36A	0.720	0.715	0.735	0.755	0.775	0.785	0.800
	6.05	5.60	5.50	5.90	6.15	6.65	7.15
	0.40	0.70	0.75	0.80	0.85	0.85	0.85
	1.50	1.30	1.15	1.25	1.20	1.10	1.20

autolysis both in the figures for depression of the freezing-point as well as for non-coagulable nitrogen; one (36A) did not autolyse during the first three hours according to the nitrogen figures,

[8] The upper left-hand figures represent degrees of depression of the freezing-point the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of $N/10$ acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of $N/10$ acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of $N/10$ alkali.

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the depression of the freezing-point only indicating an inhibition for the first hour only. It is questionable whether an autolytic latency existed here.

The following classification of experiments in the five series will indicate the results at a glance.

Conditions of Experiments	Latent Period		
	Positive	Negative	
Unwashed, well-fed, cold saline	4	0	Series I
Unwashed, fasted, cold saline	2	0	Series II
Unwashed, well-fed, cold saline	1?	1	Series II
Washed, fed, cold saline	0	1	Series III
Washed, fasted	..	1	Series III
Washed, fed, warm saline	1	3	Series IV
Washed, fasted, warm saline	0	3	Series IV
Unwashed, fed, warm saline	1?	3	Series V
	7+2?	12	

Positive Latent Period			
Fed	5+2?	Fasting	2
Cold saline	6+1?	Warm saline	1+1?
Unwashed	6+2?	Washed	1

From the tabulation it will be seen that out of twenty-one experiments nine showed a latent period; in two of these however the latency lasted only one hour so that these have been given a question mark. Of the nine positive experiments seven occurred with well-fed animals and only two in fasting ones. These results are somewhat in agreement with Schryver. Again seven of the positive latent periods occurred in experiments where cold saline was employed as diluent. Schryver employed small amounts (4 grams) of material for his experiments. This would cause a rapid lowering of temperature with consequent inhibition. Whether this author used a cold or warm diluent is not stated, and the organs were not washed.

Perhaps some importance may be attached to the fact that five of the nine positive results occurred as the first five experiments performed when the time between the removal of the organ and commencement of the autolysis was somewhat longer than in the latter experiments when our general technique had improved. In this connection it is proper to state that of twenty-five other and similar experiments reported below only four showed a latent period before autolysis and of these cold diluents were employed in three cases.

In view of these facts and of the fact that of thirteen latent periods, nine were in experiments where cold diluents were used, it is evident that the low temperature of the mixture acts as an inhibitory factor in causing a latent period of autolysis until the material becomes warmed throughout to body heat. The presence

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of blood in the unwashed organ adds an additional factor to the inhibiting forces.

Upon the whole, therefore, it seems that the latent period is most prone to appear in unwashed livers where cold diluent is employed and in those cases in which the animal was previously well-fed. It seems however, that in the light of all the experiments herein presented, it becomes questionable whether the feeding of the animal and the consequent condition of the liver possesses any direct influence on the latency of autolysis.[9] In this it is impossible to agree with Schryver nor does the latter's reasoning in regard to the liberation of enzymes in the fasting condition seem plausible. There does not exist at present, any evidence which points to any qualitative difference in the enzymic condition between the metabolism of well-fed and fasting animals. The statement that in fasting, autolytic processes by causing decomposition supply the needs of the body by the utilization of the degenerative products simply amounts to placing a well established fact in new terms, since it is very difficult to draw a sharp line between the normal analytic processes by which energy is liberated and those of autolysis associated with the death of the cell. It would appear that the question was more one of a disturbed quantitative equilibrium of the cell than of any qualitative enzymic differences.

EFFECT OF CONDITIONS UPON THE RATE OF AUTOLYSIS.

The previous discussion has had to do with autolysis within the first three or four hours after the removal of the organ from its circulation. The fact that the results indicated that the latent period was relatively inconstant and dependent upon a variety of factors led to the attempt to study first, the rate of autolysis within the first twelve hours and second, the effect upon it of altering certain conditions in the experiment in the hope that the onset of changes favoring autolysis might be inhibited. This consisted mainly in endeavoring to continue the alkalinity of the cell by means of alkaline phosphates.

Nutritional State of the Cell.—One of the most important factors to be considered in the elucidation of the origin and rate of autolysis consists in the determination of the level of equilibrium

[9] As explained later in the paper, the nutritional state of the cell may indirectly cause autolytic variations.

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upon which the cell exists at the time of stoppage of the circulation. We look to the diet of the animal as one of the most ready means of normally altering this condition and yet it becomes one of the most difficult to control, since no two animals react similarly to diet or to fasting.

The fat content of the livers of normal animals under the same diet varies as greatly as does the power of individuals to lay on subcutaneous fat.

The appearance or absence of glycogen serves perhaps as best evidence concerning the condition of the cell from the standpoint of nutrition and it is usual to conclude that the tissues are actually in a state of undernutrition when the liver is free from glycogen. Well-fed animals usually possess organs containing more or less glycogen, but even here exceptions exist and frequently animals after a long period of excessive carbohydrate diet do not show glycogen in their livers.

Concerning variations in the nitrogenous content of the liver, it becomes more difficult to make definite statements. Pearce and Jackson (12) showed that as the result of incipient necrosis or starvation from lack of circulation the cells involved lay on nitrogenous compounds in the same way as they do fat. This was in agreement with the results of Seitz (13) obtained under normal conditions. Schryver states that the liver of a fasting dog contains more non-coagulable nitrogen than that of a well-fed animal. In the experiments here reported a great variation in the amount of initial non-coagulable nitrogen exists. The average figure for twenty experiments upon fasting animals compares within one per cent. of that for eighteen well-fed animals. Selecting two cases (Experiments 25 and 26) in each of which there are three controls it is evident that no difference exists. It is not possible therefore to confirm Schryver's statement in regard to differences in nitrogen.

From a consideration of the initial figures for the depression of the freezing-point in twenty-nine experiments in which physiological saline was employed as diluent it is evident that the fasting liver possessed the lowest concentration. Eleven washed organs of which six were fasting and five well-fed and eighteen unwashed organs, seven fasting and eleven well-fed gave averages as follows:

Washed, fasting 0.475° (310–560)	Unwashed, fasting 0.609° (575–660°)
Washed, well-fed 0.594° (555–660)	Unwashed well-fed 0.664° (515–735°)

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These figures seem sufficiently definite to indicate that as far as ionic concentration is concerned the fasting animals[10] liver showed the lowest figures whether washed or unwashed. The maximum and minimum effects are indicated in Experiments 25 and 26. Experiment 25 was an unwashed well-fed liver and gave, $\Delta = 0.730$ (average three controls) while Experiment 26 with washed and fasting organs, $\Delta = 0.555$ (average three controls). In all instances the washing of the organ decreased the ionic strength of the tissue; this procedure seemed to have little effect however upon the initial acidity or alkalinity. From the fact that perfusion of an organ causes a decreased ionic concentration which is not paralleled by changes in reaction, it seems probable that the ionized substances in the cell which impart its so-called alkaline reaction are of such a character (ionized protein) that interchange or osmosis through the endothelium does not readily take place.

There are no data obtainable from the results presented in this paper which can be of service in explaining the effect of these variable nutritional conditions of the cell upon the latent period and rate of autolysis. The cursory outline above serves merely to bring to mind possible variations in cell equilibrium as regards the carbohydrates, fats, proteins, osmotic concentration, etc. This phase of the subject will receive further consideration in the final discussion as to the cause of and variations in the changes in the reaction of the cell occurring at its death.

Light.—The first external change in condition which usually occurs in tissues undergoing incipient autolysis *in vitro* and which is not in accordance with autolysis *in vivo* consists in the placing of the material in the light. Two experiments (25 and 26)— one a well-fed and the other a fasting animal—were consequently performed in which the liver was removed in the dark and two of the samples (25A and B and 26A and B)[11] autolysed in the absence of light. The third sample (25C and 26C) as control, underwent autolysis as usual. These experiments continued for seven and one-half hours. The results (Table IV) indicate that the presence of ordinary light exerts no appreciable influence upon autolysis. The increase of the depression of the

[10] Animals were given water *ad libitum*.

[11] Experiments 25A and 26A differed from 25B and 26B in that in the former a warm diluent was employed. Experiments 26A and 26C appear as the last two upon Table II; Experiments 25A and 25C, as the first two in Table III.

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TABLE IV.[12]

Autolysis in the Dark; Cold Saline (Control)	Control	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours
Exp. 25B	0.735 4.80	0.755 5.50	0.765 5.65	0.780 5.85	0.810 5.95	0.820 6.00	0.835 6.10
Not washed well-fed	0.40 0.65	0.50 0.70	0.65 0.85	0.60 0.80	0.65 0.85	0.70 0.80	0.75 0.85
Exp. 26B	0.550 5.20	0.550 5.35	0.560 5.85	0.575 6.10	0.590 6.60	0.615 7.15	0.630 8.00
Washed; not fed	0.35 0.55	0.30 0.65	0.50 0.80	0.60 0.70	0.70 0.65	0.95 0.85	1.00 1.05
Washed; Not fed	**Control**	**2 Hours**	**4 Hours**	**6 Hours**	**8 Hours**	**10 Hours**	
Exp. 29R	0.325 4.50	0.365 5.70	0.395 5.75	0.435 7.45	0.485 10.10	0.565 15.50	
Warm saline	0.45 0.75	0.80 0.80	1.10 0.75	1.40 0.90	2.50 0.95	2.95 1.95	
Exp. 29P	0.310 4.80	0.330 5.90	— —	0.385 6.45	0.390 7.40	0.395 8.00	
Warm saline and toluol	0.45 0.70	0.85 0.85	0.80 0.85	0.85 0.90	0.90 0.85	1.05 0.90	
Unwashed; well-fed	**Control**	**1 Hour**	**3 Hours**	**5 Hours**	**7 Hours**	**12 Hours**	
Exp. 31C	0.530 6.10	0.590 6.20	0.625 6.35	0.660 7.00	— 7.60	1.020 10.70	
Warm saline	0.50 0.70	0.60 0.80	0.75 0.65	0.85 0.60	0.90 0.80	1.45 0.95	
Exp. 31B	0.515 5.35	0.530 5.80	0.600 6.25	0.620 6.70	0.635 7.00	0.690 8.50	
Warm saline and chloroform	0.5 0.90	0.60 0.85	0.70 0.80	— —	0.95 1.35	1.95 3.35	

freezing-point, increase of non-coagulable nitrogen and change in reaction ran parallel in both experiments. The differences which one experiment showed as against the other as the result of the feeding of the animal, will be considered later.

Antiseptics.—Autolytic experiments as usually conducted in order to insure complete asepsis entail the employment of antiseptics such as toluol, chloroform, etc. The results of Lang (14), while not very complete, indicate that germicidal agents are not without effect upon the activity of the enzymes in autolysis. Wells and Benson (7) however incline to the view that with certain precautions, chloroform may be employed without inhibitory effect. It is evident that where comparative results are to be

[12] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of $N/10$ acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of $N/10$ acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of $N/10$ alkali.

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obtained, this variable factor should be eliminated. In this work antiseptics were not employed except in Experiments 29 and 31. In the former toluol was utilized and in the latter, chloroform. A glance at the figures in the tables will be sufficient to indicate the inhibitory action of the antiseptic, apparently more potent in the case of toluol than of chloroform. This is evident both in the figures for the depression of the freezing-point and for the non-coagulable nitrogen. Experiment 29 ran for ten hours during which time the depression of the freezing-point increased in the mixture without toluol from 0.325° to 0.565°; while in the toluolized autolysis it increased from 0.310° to 0.385°. In Experiment 31 the similar figure for twelve hours duration are with chloroform 0.515° to 0.690°; without chloroform 0.530° to 1.020°. The nitrogen increase paralleled them closely.

Reaction.—It has been quite definitely decided as the result of the work of many investigators (15) that acids accelerate and alkalies inhibit the rate of autolysis. In the majority of the experiments conducted by these workers a concentration of H + or OH-ions has been employed which is out of all accord with that possible in the cell of the animal body. The blood and protoplasm are from the standpoint of physical chemistry considered as neutral (4); very slight variations from this condition may cause profound alterations in the general metabolic process. It seemed therefore, of more value from a comparative standpoint to attempt to vary the so-called acidity and alkalinity relations of the cells in ways which more closely simulate the normal.

The immense importance which the phosphates play as regulating mediums for reaction in the body has been of late repeatedly emphasized. Mixtures of the mono-hydrogen and dihydrogen salts may be appropriately made so that the resultant solution is either neutral, alkaline or acid.[18] Hence disodium monohydrogen phosphate was employed as diluent in the hope of increasing the "alkalinity" of the tissue while the dihydrogen monosodium phosphate promised to augment the "acidity." A further method employed for the latter purpose consisted in the addition of pure neutral ethyl butyrate to the autolytic mixture. As autolysis proceeded the lipolysis of the butyrate set free butyric acid, thereby increasing the acidity markedly. This reaction may also be

[18] In relation to phenolphthalein. Henderson (4) has shown that in solutions of these two salts great variations in their relative proportions may exist without changing the H + concentration to any great degree.

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supposed to take place in the living cell but ordinarily sufficient bases are at hand for neutralization. In autolysis (lipolytic) should the bases be lacking the H^+ concentration would be increased.

An examination of the figures obtained for the control samples as indicative of the character of the initial state of reaction of the tissue indicates that either the method of titration with the two indicators is too crude to show slight variations which might occur in the living tissue, or the factors which influence the reaction of the tissue and which would aid in explaining the results, are unknown. Certain differences in the figures for the controls under the various conditions did appear but no one condition which has been discussed here is apparently accountable for the changes.

In Experiments 23, 28B, 30A, 32C, 33B and 36 (Table V) attempts were next made to increase the alkalinity of the reaction of the mixture in which autolysis was to occur by means of disodium hydrogen phosphate in five per cent. solution and Experiment 28C by alkaline Locke's solution.[14] It is interesting to note that while the disodium phosphate was *alkaline* to phenolphthalein (0.8 c.c. $N/10$ acid for 10 c.c. of solution) and alkaline to dimethylaminoazobenzene (10.65 c.c. $N/10$ acid for 10 c.c. of solution), when the autolytic mixture of this solution and tissue was analyzed, the mixture possessed the *acidity* to phenolphthalein ordinarily found when sodium chloride is employed as diluent. Unfortunately, it is impossible to say from the methods employed just what physical changes occurred when the tissue and phosphate solution were mixed. From the chemical standpoint of reaction the tissue transformed the alkaline solution (phenolphthalein) to one which reacted acid. The explanation for this probably lies in the rearrangement of phosphates in the solution by which the large excess of disodium hydrogen phosphate reacted with acid factors in the tissues and became transformed into sufficient dihydrogen sodium phosphate to cause the autolytic mixture to assume its normal reaction. This forms simply another manifestation of the regulating mechanism described by Henderson (4). All attempts therefore to increase in this manner the alkalinity (phenolphthalein) were negative and the results

[14] Locke's solution to which was added sufficient sodium bicarbonate to bring the strength of the salt up to 0.5 per cent.

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TABLE V.[15]

5 Per Cent. Na_2HPO_4.	Control	1 Hour	3 Hours	6 Hours	8 Hours	10 Hours
Exp. 23 Washed; well-fed; cold diluent	0.525 — 1.45 11.50	0.520 5.30 1.90 11.35	0.560 5.60 2.00 11.30	0.610 5.80 2.25 11.80		
Exp. 28B Unwashed; not fed; warm diluent	0.530 4.30 0.65 11.45	0.545 5.60 1.00 11.25	0.615 7.10 1.40 11.40	0.640 7.75 1.65 11.80		
Exp. 30A Unwashed, not fed; 10 *per cent.* warm diluent	0.685 6.70 0.70 21.75	0.710 6.65 1.00 21.65	0.745 6.50 1.05 20.90	0.780 7.65 1.15 20.95	0.795 — 1.70 20.05	0.900 12.45 2.40 19.50
Exp. 32C Unwashed; not fed; cold diluent	0.735 — — —	0.705 — — —	0.705 — — —	0.715 — — —		
Exp. 33B Unwashed; not fed; cold diluent	0.700 8.55 0.90 10.3	0.730 8.15 1.10 10.6	0.740 8.20 1.60 10.1	0.790 8.80 2.50 9.65		
Exp. 36 Unwashed; well-fed warm diluent	0.910 6.15 0.90 13.1	0.900 6.40 1.2 14.9	0.950 6.90 1.55 13.05	0.995 7.55 1.75 12.65		1.620 17.55 17.55 26.4
Exp. 28C Unwashed; not fed; warm *Alkaline Locke's solution*	0.680 5.60 1.60 1.15	0.700 4.40 1.70 1.15	0.785 4.65 1.85 —	0.795 4.80 1.7 1.50	0.805 4.60 1.75 1.25	
Exp. 32B Unwashed; not fed	0.650 — —	0.660 — —	0.650 — —	0.650 — —		
Cold Na_2PO_4	—	—	—	—		

of these experiments do not differ from those reported with saline as diluent.

One experiment performed with Locke's solution made alkaline with 0.5 per cent. sodium bicarbonate[16] (28C) ran seven and one-half hours. In this instance also the resultant mixture of liver and bicarbonate solution became acid to phenolphthalein and alkaline to dimethylaminoazobenzene. In fact the respective acidity and alkalinity was greater in each case than with sodium chloride. Undoubtedly a reaction occurred between the phosphates of the cell and the sodium bicarbonate, carbon dioxide being liberated, and in this way increasing the acidity to phenolphthalein.

[15] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

[16] Of this solution, 10 c. c required 0.15 c.c *N*/10 acid to neutralize to phenolphthalein and 1.55 c.c. to dimethylaminoazobenzene.

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The increase in depression of the freezing-point[17] was about that observed in other experiments, where a similar reaction was present; no inhibition or latent period could be noticed. An examination of the figures for non-coagulable nitrogen indicates however that no nitrogenous autolysis occurred, the figures for the end of the experiment being the same as the control or even somewhat lower. In this case no increase in acidity (phenolphthalein) took place such as ordinarily occurs with sodium chloride solution as diluent.

One experiment employing tri-sodium phosphate as diluent did not result favorably since the autolytic mixture became extremely thick and ropy. Upon heating no coagulation occurred; the mixture required the addition of such a large amount of acid before complete coagulation occurred that attempts to perform nitrogen and acidity determinations were abandoned. Unfortunately the diluent solution was employed cold so that it is impossible to decide whether the extremely long "latent" period as evidenced in the depression of the freezing-point was to be ascribed to this or to the phosphate solution. It would seem more probable that the lack of increase in molecular concentration found in this autolysis was due to the phosphate solution on account of its alkalinity (phenolphthalein) and this fact agrees with observations of previous investigators that alkalies inhibit autolysis. An alkalinity equivalent to this never occurs in the body.

In one experiment (29D) where dihydrogen sodium phosphate served as diluent, the autolytic mixture was strongly acid to phenolphthalein. This experiment should be compared with Experiment 29E (Table II, Series IV) and the control with saline. No noticeable variation in rate of autolysis can be detected.

In Experiment 33 and 36 in which pure ethyl butyrate was added to the autolytic mixture a most marked increase in acidity (phenolphthalein) was observed together with the greatest augmentation of non-coagulable nitrogen and the depression of the freezing-point obtained in any of the experiments. These two experiments ran for twelve hours and were absolutely sterile throughout. The depression of the freezing-point increased in Experiment 36 from 0.810° to 1.515° and in Experiment 33 from 0.685° to 1.285°. The non-coagulable nitrogen rose in Experiment 36 from 5.8 to 28.15 and in Experiment 33 from 3.25 to

[17] Whether this is indicative of autolysis is questionable; *c. f.*, the later discussion on this point.

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TABLE VI.[18]

	Control	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
Exp. 29D Washed; not fed; 5 per cent. H_2NaPO_4	0.635 5.05 10.95 1.85	0.635 5.30 11.7 1.75	0.680 5.50 12.85 1.95	0.725 7.40 13.05 1.75	0.765 12.40 13.50 1.60	0.795 14.35 14.05 1.65
Exp. 33C Unwashed; not fed; 1 c.c. ethyl butyrate with saline diluent	0.685 3.25 1.10 2.00	0.725 4.50 1.30 2.10	0.745 7.40 1.85 2.45	0.820 14.90 3.00 2.80	— — — —	1.285 33.85 5.10 8.60
Exp. 36C Unwashed' fed; 1 c.c. ethyl butyrate with saline solution	0.810 5.80 1.25 1.10	0.815 5.60 1.55 1.55	0.845 5.35 1.60 1.45	0.920 10.05 2.35 1.65		1.515 28.15 6.65 5.35
Exp. 27E Unwashed; not fed; warm Locke's solution.	0.625 6.25 0.40 0.75	0.650 6.10 0.60 0.70	0.670 6.10 0.80 0.70		0.705 6.50 1.00 1.00	
Exp. 31A Unwashed; well-fed; warm Locke's solution	0.630 5.60 0.60 0.40	0.720 5.65 0.75 0.75	0.775 5.60 0.85 0.75		0.800 7.20 1.15 0.85	1.015 20.8 6.80 2.7

33.85.[19] Considered from every standpoint the autolysis was most strikingly accelerated by the formation of the butyric acid during the progress of the autolysis.

In general therefore attempts to alter the rate of autolysis by means of acid and alkaline phosphates and bicarbonates resulted negatively. Some evidence was obtained that an alkaline reaction tends to inhibit the nitrogenous autolysis; this was especially well marked in Experiment 28C. The production of butyric acid during autolysis set up a marked acceleration in the rate of the decomposition.

Salt Concentration.—It seemed plausible that one of the conditions which favored the onset of autolysis might consist in the decrease in concentration of the salts (mainly calcium and potassium compounds) of the tissue as the result of the dilution with sodium chloride and phosphates. Such a condition would of course be accentuated in a perfused organ since during the irrigation the calcium, potassium, and other salts would diffuse out from the cell into the perfusing solution.

[18] The upper left-hand figures represent degrees of depression of the freezing-point; the upper right-hand figures, non-coagulable nitrogen expressed as cubic centimeters of *N*/10 acid; the lower left-hand figures, acidity to phenolphthalein in terms of cubic centimeters of *N*/10 acid; lower right-hand figures, alkalinity to dimethylaminoazobenzene in terms of cubic centimeters of *N*/10 alkali.

[19] In Experiment 36 it is noticeable that the acidity did not increase very rapidly during the first four hours and that the nitrogenous autolysis suffered a latent period.

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In order to partially avoid such diminished concentration, in two experiments (27E and 31A) Locke's[20] solution was added as diluent and the autolytic rate studied. Although the results show an increase in ionic concentration, the figures for the non-coagulable nitrogen are plainly indicative of a lack of autolysis existing up to the fifth hour. While one cannot draw too definite conclusion from the results of only two experiments, it seems reasonable to believe the retaining of the salt content of the tissue in approximately unchanged concentration, acts as another factor tending to inhibit or at least to retard nitrogenous autolysis. It is also probable that the Ca or K ions are in some way active in this regard, and that the difference in rate of autolysis noticed between washed and unwashed organs can be ascribed to this cause in part.

This question was attacked in another way. The tissues were aseptically removed and allowed to autolyze *en masse* in the thermostat and then diluted as usual with three volumes of physiological saline. Unfortunately no figures for non-coagulable nitrogen were obtained in this series.[21]

The depression of the freezing-point for the tissue itself and the diluted mixture increased in about the same rate as in all other experiments.

DISCUSSION.

The two procedures employed for the determination of the inception and rate of autolysis have been utilized previously by several investigators. The increase in non-coagulable nitrogen was the first test applied in this direction since it was early recognized that in the autolytic hydrolysis the coagulable nitrogen of the protein became changed into nitrogen of substances which were of smaller molecular weight and could not be rendered insoluble by heat. More recently however the attempt to control this procedure by other methods has resulted

[20] When physiological saline is employed as diluent, the osmotic concentration of the tissues is supposed to continue the same as when the blood is circulating through the organ. The percentage concentration of the salts other than sodium chloride is nevertheless markedly diminished. Locke's solution which approaches the blood as regards its content of inorganic salts was utilized for this reason.

[21] For this reason the study of this type of experiment is to be continued more particularly with reference to possible differences in the rate of autolysis after the organ has been prepared by perfusion *in situ* with solutions of various types of salts, and in this way the attempt may be made to alter the conditions existing in the cell before the commencement of autolysis.

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in the determination of the electrical conductivity and of the molecular or ionic concentrations of the solutions undergoing autolysis. If we are dealing with autolytic mixtures of pure protein, hydrolytic changes occurring in the solution would make themselves evident by all three methods, but not simultaneously, since in the initial stage of the reaction the proteins would become transformed into proteoses or non-coagulable nitrogen, without any decided augmentation in molecular or ionic concentration sufficient to effect the depression of the freezing-point or electrical conductivity. Toward the end of autolysis the maximum proteose nitrogen might be reached while progressive hydrolysis would continue to break down the molecules still further with consequent increased molecular concentration thereby affecting the depression of the freezing-point. The electrical conductivity on the other hand could only be increased by the formation of ionized molecules. From this it is evident that even in a simple solution of protein these three factors might not run parallel.

In the cell however the process becomes still more complex. Autolysis of non-nitrogenous substances such as glycogen, the lipoids, neutral fats and the rearrangement of inorganic salts would set up changes in molecular and ionic concentration which would not be indicated by a study of variations in non-coagulable nitrogen. It is hard therefore to agree with the statement of Wells that determinations made of these three factors (non-coagulable nitrogen, depression of the freezing-point and electrical conductivity) parallel one another. That they might do so must be admitted; that the chances are very much against their doing so is most probable.

A general survey of the results obtained in this investigation presents much evidence in favor of the latter view. In some experiments (5b, 10, 22, 23, 27E and 28A and 28C) conclusions would be reached from the figures obtained from the non-coagulable nitrogen that no autolysis had occurred up to the sixth or eighth hour. In fact in Experiments 28A and 28C less non-coagulable nitrogen was present in solution at the end of seven and one-half hours than in the control at the outset of the experiments. One could naturally assume that non-coagulable nitrogen had become synthetized into protein nitrogen. The figures for the depression of the freezing-point, however, show that the molecular or ionic concentration was increasing gradually up to the end of the experiments. This is especially well marked in

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Experiment 28C, where depression of the freezing-point increased from 0.680° (control) to 0.805° (seven and one-half hours). Evidently non-nitrogenous molecules were undergoing hydrolytic cleavage with the production of smaller and more numerous molecules.

We do not have to look far for an explanation of these results. It has been mentioned elsewhere that with apparently the same conditions of diet, the liver of dogs varies markedly in the content of fat and of glycogen and there is also variation in the rapidity with which the latter disappears. With these points in mind a study of the notes taken in various experiments plainly brings out the fact that in those cases where the glycogen disappeared most rapidly as deduced by the decrease in opalescence of the filtrate after heat coagulation, the depression of the freezing-point tended to increase regardless of changes in non-coagulable nitrogen. In the absence of glycogen the depression of the freezing-point was not affected in this manner. Evidently the increased depression of the freezing-point occurred in greatest part at the expense of the hydrolysis of glycogen, the latter being transformed into smaller molecular compounds, such as maltose, lactic acid, etc.

Concerning lipolytic changes, it becomes more difficult to determine what part these processes are playing in the whole general autolytic change, since there is no way of visually following the transformation as is the case with glycogen. Increased acidity in the autolytic mixture may be the result of the hydrolysis of fats or equally well of the carbohydrates. It therefore is of the utmost difficulty to decide to what process is due the increased acidity as determined by phenolphthalein. From the fact that in a majority of the experiments there occurred a gradual increase in acidity (phenolphthalein) associated with no simultaneous changes in reaction to dimethylaminoazobenzene, it seems reasonable to consider that the augmented acidity was not brought about by increase in acid phosphates since dimethylaminoazobenzene would react to such change; but rather to a formation of acids of the fatty acid type to which the latter indicator is not sensitive.

In this connection emphasis must be laid upon the results of the two experiments in which ethyl butyrate was added to the autolytic mixture. The pronounced acceleration of autolysis which occurred evidently as the result of the formation of butyric acid in the mixture cannot fail to have but one significance. Given

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a cell in which as the result of increased lipolysis from some reason or other fatty acids are being produced in excess, their presence will markedly stimulate nitrogenous autolysis. The fat and fatty acids content of supposedly normal cells vary within very wide limits. This is a factor which must be reckoned with in the consideration of general or even nitrogenous autolysis. Whether the augumented autolysis is a result of the catalytic action of the hyrodgen ions of the butyric acid or whether the same relationship exists between the lipolytic autolyses and the decomposition of protein substances, is hard to decide.

From this somewhat cursory discussion it becomes evident that at the time when the cell becomes removed from its circulation, hydrolytic changes are set up with varying degrees of rapidity; the character of these changes is dependent upon the condition of the cell at the time. The reaction of the fluids bathing the protoplasm (if the protoplasm is considered to be neutral) is an important factor as shown by the many investigations upon the effect of acidity and alkalinity upon autolysis. The results recorded here plainly indicate however that changes in reaction which most nearly simulate those which can occur in the living cell do not alter the autolytic rate so markedly, if they do at all, as where stronger acids and alkalies are employed.

In the majority of cases only the nitrogenous autolysis has been studied. As it has been indicated, if carbohydrates are present in the cell, amylolytic autolysis will also occur; lipolytic autolysis probably is as constant as the nitrogenous process. Either one of the three types of autolysis may occur without the other. Probably all three originate when general autolysis begins. That one process influences the others and that the products of the autolytic hydrolyses (lactic acid, fatty acids, etc.) markedly influence, per haps augments the others (*e. g.*, nitrogenous autolysis) are facts rapidly being brought into prominence. Further study in this direction should lie in attempts to test the effect upon autolysis of a single type, *e. g.*, nitrogenous, by setting up simultaneously in the mixture amylolytic or lipolytic autolysis; this would also include the effect of autolytic products, upon the rate of all three types of autolysis.

CONCLUSIONS.

1. Under certain conditions, general autolysis does not begin immediately upon the removal of the organ from its circulation.

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This latent period is more apt to be present in those cases in which the tissues have been temporarily cooled on account of the use of a cold saline diluent or in which the percentage concentration of the inorganic salts (calcium or potassium), of the tissues have been changed by dilution with a sodium chloride solution. The presence of blood and absence of fats and of glycogen in the cells act as important factors in prolonging the latent period.

2. Attempts to produce an alkaline reaction (phenolphthalein) in the tissue resulted negatively. Solutions of disodium hydrogen phosphate and of sodium bicarbonate when added to the liver tissues gave a mixture which was acid to phenolphthalein and no effect upon autolysis was apparent.

3. The addition of antiseptics—chloroform and toluol—markedly decreased the rate of autolysis. Ordinary light produced no effect.

4. Ethyl butyrate when added to the tissue became hydrolysed into butyric acid; the formation of this acid in the mixture caused a decided acceleration in the autolytic rate. The acidity of a solution of dihydrogen sodium phosphate failed to produce a similar result.

5. The figures for the changes in the depression of the freezing-point, non-coagulable nitrogen and reaction of the autolytic mixture do not parallel one another. In some experiments a marked increase in the depression of the freezing-point was unaccompanied by augmentation of non-coagulable nitrogen.

6. General autolysis is the sum total of proteolytic, amylolytic and lipolytic factors. Each of these autolytic factors may proceed alone for a time; the rate of one is decidedly influenced by the presence or absence of the others. The acid products which are the result of amylolytic (lactic acid) and of lipolytic (higher fatty acids) autolysis, exert a pronounced augmentative effect upon the commencement and rate of nitrogenous autolysis.

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THE INFERIOR LONGITUDINAL BUNDLE AND THE GENICULO-CALCARINE FASCICULUS. A CONTRIBUTION TO THE ANATOMY OF THE TRACT-SYSTEMS OF THE CEREBRAL HEMISPHERE.

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Ever since Burdach's time, the most external of the three sagittal layers which surround the descending and posterior horns of the lateral ventricle and which form the deep boundary of the central white matter of the temporo-occipital lobe, has been known as the inferior longitudinal bundle and considered as being composed essentially of association fibres uniting the cortex of the occipital lobe with that of the temporal lobe. More recently Sachs has proposed the term *stratum sagittale externum* for this layer of fibres and the latter denomination has gradually superseded the old one in the more modern text-books on the anatomy of the brain. But, by whatever term this mass of fibres may have been designated, the majority of observers have at all times been unanimous in regarding it as an association tract. We do not intend to analyze here the views held by the different anatomists; this being our fourth contribution to this particular chapter of nervous anatomy and an exhaustive review of the literature of the subject having figured in our original monograph[1] on the central optic or geniculo-calcarine fasciculus in 1906. We will content ourselves with recalling that Burdach's conception of the inferior longitudinal bundle has, with certain modifications of a purely anatomic order bearing upon details of morphology, relationship, etc., been shared by Arnold, Sachs, Déjerine, von

[1] Nouvelle Iconographie de La Salpêtrière, 1906, No. 1, p. 103 and No. 2, p. 178.

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Monakow, Obersteiner, Schellenberg, Edinger, Schaffer and others.

Flechsig was the first to oppose on the basis of a well-established anatomic principle, the sense of the classic doctrine regarding the physiologic character of Burdach's bundle. As the result of his researches upon the embryology of the central nervous system, more particularly with reference to the period at which the various nerve-tracts become invested with myelin, he was led to contend in 1895 that the inferior longitudinal bundle is made up exclusively of projection fibres derived from the optic thalamus (inferior segment of the lateral nucleus and main nucleus of the pulvinar) and terminating in the occipital lobe, more particularly in the visual area. After emerging from the optic thalamus, the fibres of this tract are intermingled with others having the same source and destined to the olfactory area and Ammon's horn, and with still other fibres coming from the internal geniculate body and optic thalamus and coursing to the temporal lobe and to the auditory sphere. Flechsig's doctrine soon gained hearty support and the later contributions of Probst, Niessl-Mayendorf, Redlich and others brought it abundant confirmation.

Within the last five years, a few authors (Starokolitzki, Weber) have arisen as pacificators to adjust the ominous differences between the old and the new School and have taken the very safe stand of ascribing to the inferior longitudinal bundle a mixed character, i. e., they claimed that it contains both projection and association fibres.

We were not able to view thus the constitution of the aforenamed tract and favored entirely the new doctrine which proclaims it a purely projection fibre-system. But there our task could not end, as there still remained wide differences between Flechsig's followers as regards the exact source, course, termination and physiologic significance of the total mass of fibres which go to make up the inferior longitudinal bundle.

Personally, we believe that all the constitutent fibres of the inferior longitudinal bundle are of the projection variety, but hold that this bundle represents not one but several individual tracts comprising both corticifugal and corticipetal fibres and that its constitution varies from one level to the other. Our main object has been, and still is, to isolate from the great mass of fibres which compose the inferior longitudinal bundle, a certain

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contingent of appreciable magnitude, and to clearly demonstrate its existence as a perfectly well-defined anatomic entity. The perfect autonomy of this fasciculus was revealed to us in the course of our researches upon the anatomy of the brain pursued in the laboratory of our teacher, Pierre Marie, at the Hospice de Bicêtre, Paris. We had occasion to systematically examine by means of serial sections eight cases of cerebral softening with involvement, to a greater or lesser extent, of the constituent fibres of the inferior longitudinal bundle. In the majority of the cases, the lesions were those characteristic of sensory aphasia (lesion of the supramarginal and angular gyri and of the bases of the first and second temporal convolutions). In one case, we had the exceptional good fortune of having to do with a strictly cortical patch of encephalomalacia extending over a considerable antero-posterior area without implication of the deep sagittal layers. Our results were constant. We found that a significant proportion of the longitudinal fibres of Burdach do not take their origin from the occipital lobe but from some anterior level, as they were always seen to degenerate caudad, i. e., behind the seat of lesion, and furthermore, that their source is not from the cortex of the temporal lobe (thus eliminating at once the possibility of their being association fibres), as these fibres were not affected by lesions limited to the cortex and subcortical substance of this lobe. In one case the entire occipital cortex and subcortex were destroyed and in the depth of the lobe one fasciculus was discernible and relatively intact, it was Burdach's inferior longitudinal bundle, which, at this level, constitutes likewise the external sagittal stratum. The only conditions under which we observed the degeneration of the inferior longitudinal bundle in the occipital lobe were: (a) the direct section of the deep sagittal layers at anterior levels, and (b) the existence of lesions of the lenticular nucleus, the external geniculate body and adjoining portion of the optic thalamus. In judging of the integrity or implication of this contingent of the inferior longitudinal bundle, it is with intent and purpose that we choose the occipital lobe as the field of decision, as we have ever and still deem it indispensable to make ourselves clear regarding the exact proportion of inferior longitudinal fibres which we wish to identify under the name of central optic or geniculo-calcarine fasciculus. Ambiguity creeps in unnoticed, and misinterpretation, while a pardonable offense, is one which is often extremely difficult to

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expose. We have already had to seriously contend with the pernicious effects of misquotation and are therefore anxious, even at the cost of repetition, to obviate all possibility of further misconstruction. This preliminary explanation is all the more important owing to the laxity with which the terms "inferior longitudinal bundle" and "stratum sagittale externum" are used synonymously. We have from the very outset insisted upon the fact that the term tract or fasciculus should be restricted to the designation of a bundle of nerve-fibres coursing over an appreciable distance and the territory of which remains fairly well defined throughout. The word stratum has a much wider range of application and implies little more than mere regularity of disposition of a great mass of nerve-fibres at any one point. That in the occipital lobe the distinction between these terms may have but little significance, we readily admit, but it is all otherwise in the temporal lobe, and especially in its middle portion where the retrolenticular segment of the internal capsule comes into view. At this point, indeed, the external sagittal layer contains both corticipetal and corticifugal projection fibres, it likewise harbors a certain number of association fibres. Still farther forward, the external sagittal layer is traversed by the congregating fibres of the anterior commissure, it becomes blended below the sphenoidal horn with the temporal segment of the cingulum and laterally with the innermost fibres of the fasciculus uncinatus. So that it becomes evident on all hands, that the stratum sagittale externum of Sachs varies in its constitution from one level to the other, that in the temporal lobe it differs materially from the stratum sagittale externum of the occipital lobe, and that, taken as a whole, it does not correspond to the classic description of the inferior longitudinal bundle.

What we desire to clearly establish is that the external sagittal layer of the occipital lobe, the inferior longitudinal bundle such as it exists in this lobe, is composed exclusively of projection fibres. For us, this layer represents the corticipetal complement of the occipital corona radiata; its constituent fibres take their origin from the external geniculate body and terminate in the cortex bordering upon the calcarine fissure. In order to avoid useless errors of interpretation we proposed for this contingent of projection fibres the name of "central optic" or "geniculo-calcarine fasciculus"; the latter term being more in harmony with the nomenclature recently introduced by Edinger, and

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which, on account of its simplicity and anatomic significance, is fully deserving of speedy and universal acceptation.

We cannot, in this connection, dwell at any length upon the facts brought out in our previous publication, regarding the true character of the inferior longitudinal bundle. We shall have abundant occasion in giving a detailed description of three additional corroborative cases of cerebral softening, to refer to many facts already signalized in our first monograph, to emphasize some and to elucidate others. But before we proceed with the actual study of these cases, it would be well perhaps to reproduce here our original conclusions regarding the inferior longitudinal fasciculus. We transcribe literally from our article in the *Nouvelle Iconographie de la Salpêtrière* (1906, No. 2, p. 215):

(1) There exists a nerve-tract, the component fibres of which occupy in the temporal lobe, partly the external, partly the internal sagittal layer, and which, in the occipital lobe, constitute almost the whole of the external sagittal layer. This tract, which represents the corticipetal corona radiata of the occipital lobe, takes its origin from the external geniculate body and terminates in both the upper and lower lips of the calcarine fissure, but more particularly in the latter. We propose for this bundle of fibres, the name of "central optic fasciculus" or better still that of "geniculo-calcarine fasciculus."

(2) This tract should be differentiated from the association fibres which constantly invade its territory. If for the sake of simplicity, usage will have it that all fibres which merely traverse a nerve-tract form part of it, we shall say that the inferior longitudinal bundle of the classic authors comprises: (a) the central optic fasciculus, and in addition (b) a certain number of association fibres.

(3) However extensive a lesion of the occipital lobe may be, a normal aspect is resumed at the level of the anterior temporal region, and we do not recognize the existence in man of the long association fibres of classic writers.

Recently, in a very interesting and instructive article, Adolf Meyer[2] brings forth additional data of unquestionable significance in demonstrating the correctness of Flechsig's view, that the external sagittal layer, or marrow, as he calls it, is constituted solely

[2] Transactions of the Association of American physicians. Twenty-second Session, 1907. Volume XXII. Philadelphia, 1907.

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by projection fibres derived from the basal ganglia and coursing for the most part to the occipital lobe, particularly to the calcarine cortex. But Meyer falls into error when he attributes to Flechsig the designation of these fibres by the term "geniculo-calcarine tract." We have already seen that this author regards the optic thalamus as the starting point of the external sagittal layer; prudent and circumspect he does not grant the entire domain of this layer to the fibres destined to the visual area, wherein he differs materially from Meyer, but includes the fibres going to the temporal lobe, more particularly to the auditory and olfactory areas. I believe that I may be credited with having introduced the term "geniculo calcarine fasciculus" and I am sure that I did not employ it as a synonym for the external saggital layer in its entirety, but for its occipital segment only. Meyer makes it a point to dwell upon a case which, in his opinion, incidentally serves to correct a claim raised by me that retrograde degeneration does not occur and that its appearance is produced by a lesion in the lenticular region. He refers to a lesion which consists of a destruction of the posterior end of the calcarine area and an undermining of the more anterior parts of the temporo-occipital base far into the fusiform gyrus, from occlusion of the posterior cerebral artery. The actual softening reaches far into the optic radiations beyond the lateral angle of the ventral segment and into the height of the dorsal segment and it destroys completely the posterior end of the lateral radiation. In keeping with this the external geniculate body is practically empty; only the most dorsal radiations are preserved as a compact bundle; the rest are almost reduced to nothing. The entire ventral portion which makes the temporal détour is degenerated. No lenticular lesion accounts for the degeneration of the geniculo-calcarine tract.

In the first place, I wish to correct in my turn the author's interpretation of my statements concerning retrograde degeneration. I have not only never maintained that it does not occur but have even related two instances in which it had been personally observed.[3] What I have tried to do was merely to point out the too great laxity with which retrograde degeneration is invoked in order to easily account for otherwise unclear degenerative pictures and the danger of doing so when discussing in-

[3] Nouvelle Iconographie de La Salpêtrière, 1906. No. 6, p. 573. Nouvelle Iconographie de La Salpêtrière 1906, No. 2, pp. 185–188.

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sufficiently established fibre-systems. In the second place, in describing one of my original cases, I attributed a zone of sclerosis situated in the inferior part of the vertical segment (frontal section) of the external sagittal layer and which could be distinctly followed throughout the temporo-occipital lobe, to a destructive lesion of the lenticular nucleus, and there is no question in my mind about the correctness of this interpretation; the sclerotic field emerges from the lower angle of a completely destroyed lenticular body, and from the inner border of this nucleus, the fibres, although atrophic, stain relatively well and can be seen to curve backward and mesially towards the external geniculate body.

I am not of those who believe that the degenerative sclerosis of a given tract must necessarily always be explained by the same factor or group of factors. Lesions vary greatly in different cases as regards both their actual extent and duration. Meyer's contention that in the first case published by him (case of idiocy with total destruction of the parietal, temporal and occipital lobes of the left hemisphere, with the exception of the posterior part of the calcarine cortex including the tip of the occipital lobe), the geniculo-calcarine tract appears in pure culture seems to me inadmissible. The voluminous stratum of fibres which figures in the three plates devoted to the illustration of this case, contains, in my opinion, other fibres besides the geniculo-calcarine; fibres destinated to the first temporal convolution and to the mesial convolutions of the temporal lobe, to the gyrus hippocampus in particular. The fact that there is no temporal cortex to receive some of them is not unmistakable evidence that all of these fibres are coursing to the calcarine cortex. In fact, the same remark could, with perfect reason, be made regarding the mesial occipital cortex; there is too little of it left to harbor the great mass of relatively healthy geniculo-calcarine fibres present, and therefore to explain the persistence of this tract *en masse*. Moreover, I do not believe it indispensable that both the beginning and the end of a tract be intact in order that it may persist, but that it will do so if its nucleus of origin is intact and the tract itself is not directly involved in the greater part of its course. If it were otherwise, we would see, in Meyer's case, a far less voluminous stratum of corticipetal fibres; being given that an appreciable portion of the calcarine area is destroyed. It is even remarkable that retrograde degeneration has not, being given

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that this case is one of long standing, made its appearance in this particular instance. I am of the opinion that in Meyer's most instructive case, in the same way that a large number of geniculo-calcarine fibres are preserved despite their destination to a no longer existing segment of the calcarine cortex, so exist likewise in this persisting stratum of corticipetal fibres, a certain proportion of fibres coursing to a destroyed temporal cortex. The fibres simply terminate abruptly in the peri-focal sclerotic zone without having reached their anatomo-physiologic end-station.

Let us now take up systematically the study of the three new cases of cerebral softening referred to before and which seem to us to integrally confirm our original conclusions regarding the external sagittal layer of the occipital lobe.

Case I. Tracnard. Left cerebral hemisphere. (Pl. I) Patch of softening involving the supramarginal gyrus, the base of the first temporal convolution, the whole of the angular gyrus and the adjoining portion of the second occipital convolution.

A section carried through the occipital region at a point about one centimeter behind the splenium corporis callosi shows that the lesion has extended deeply into the white matter and destroyed all the structures bordering upon the superior wall and the upper two-fifths of the lateral wall of the ventricle. On section through the splenium, it is seen that the lesion has excavated practically the whole of the supramarginal gyrus and the first temporal convolution at their point of fusion, sparing the cortex, however, so that a mere shell of cortical substance replaces the former convolutions. The process here again extends as far as the ventricular lining in the area corresponding to the upper half of the lateral wall of the ventricle, which at this point shows decided dilatation. The tapetum and sagittal layers are therefore completely destroyed in their upper segment. More anteriorly, the lesion rapidly diminishes, becoming limited to the lower border of the supramarginal gyrus and the upper border of the first temporal convolution in the depth of the Sylvian fissure. Sections passing through the hemisphere at a point one and five-tenths centimeters behind the pulvinar of the optic thalamus reveal no appreciable foci. Small patches of recent softening are also noted along the superior border of the hemisphere, involving at some points the mesial cortex, at others, the subcortex, of the paracentral lobule and base of the superior frontal convolution; but the latter lesions do not interest us as they have no bearing upon the question under consideration and cannot, moreover, lend any element of confusion.

The first section illustrating this case (Pl. I, Fig. 1) is taken from the anterior part of the occipital lobe. The lesion at this level destroys entirely the angular gyrus and the second occipital convolution at about their point of fusion, penetrating deeply and reaching almost to the

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stratum calcarinum which stretches over the prominence (calcar avis) caused by the dipping in of the calcarine fissure. The ventricle is prematurely closed (symphysis ventriculi). The Gennari streak can be seen with unusual distinctness. The softening has destroyed the tapetum, the internal and external sagittal layers, corresponding to the dorsal or upper half of what may be termed the lateral segment of these structures. It will be seen that owing to the closure of the occipital horn, the deep layers have practically but a vertical extent and that they are divisible into a mesial and a lateral segment, between which the tapetum intervenes. In the lower part of the section and going outward from the bottom of the calcarine fissure, we can distinguish several layers regularly disposed: (1) a broad band completely degenerated which represents the tapetum, (2) the internal sagittal. layer or inner optic radiation of Flechsig, derived from the occipital cortex and coursing to the pulvinar of the optic thalamus. It is moderately and diffusely degenerated, owing, in part, to the presence of fibres derived from the lateral convolutions of the occipital pole which are themselves undermined by the softening, and, in part, to its close proximity to the lesion at this level. (3) The external sagittal layer, which in this region is constituted essentially by the geniculo-calcarine tract. The ventral segment of this tract is practically normal, as it has not been involved at any point in its course through the more frontal regions. (4) Closely investing the geniculo-calcarine fasciculus externally and almost blended with it, a narrow band may be seen on close inspection; it is distinctly degenerated and may be followed with the external sagittal layer into the depth of the lingual lobule. This outermost layer contains association fibres derived from the lateral convexity and coursing to the lingual lobule. It is thus made up of fibres which form part of the association bundles known as Wernicke's perpendicular occipital fasciculus and Vialet's transverse fasciculus of the lingual lobule. From the regularity of its disposition one would almost be tempted to describe a *stratum sagittale extremum occipitale*. It is not the first time that I see the deep association fibres of the occipital lobe assume this layer-like disposition, and this fact amply suffices, in my opinion, to explain the many difficulties encountered by the earlier writers in their attempts to define the character of the external sagittal layer. It shows once more the perplexingly intimate relationship between projection and association fibres.

Von Monakow illustrates in his work[4] the occipital degeneration in a case of cortical hemianopsia. The lesion, situated in the interparietal fissure, almost completely destroys the upper segment of the angular gyrus and the contiguous portion of the superior parietal convolution, dipping down to the ventricular ependyma of the superior wall of the occipital horn. The drawing shows a degeneration of the entire external sagittal layer (which the author calls the inferior longitudinal bundle), so that a degenerated ring practically encircles the ventricular horn. The degenerated fibres must therefore pursue a vertical course and can only

[4] Von Monakow-Gehirnpathologie p. 752. Taken from Nothnagel's Specielle Pathologie u. Therapie, IX Band, Wien 1905.

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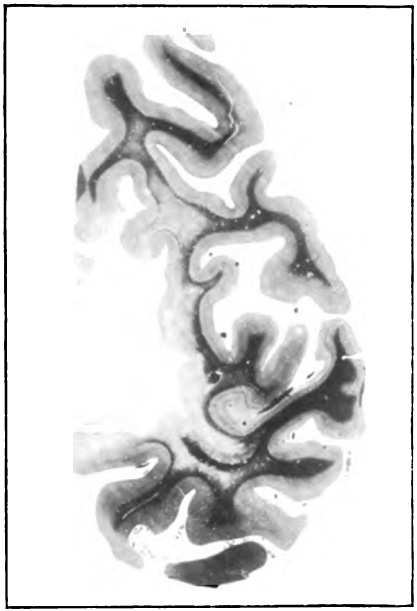
PLATE I



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represent the association fibres of the region. We know indeed from the direction of the constituent fibres of the external sagittal layer, that it is impossible for a lesion limited to the superior convolutions of the parieto-occipital convexity to determine a secondary degeneration of the total mass of its fibres. It can only react upon the fibres of its dorsal segment. It thus becomes evident that in von Monakow's case, the degenerated fibres do not form part of the external sagittal layer, properly speaking, but that they simply closely invest it externally; a conclusion, moreover, which one would readily deduce from a careful study of the drawing. It is well to recall, in this connection, that von Monakow is among those who regard the external sagittal layer as an association tract, and it may further be stated, that the same author does not recognize the existence of Wernicke's vertical occipital fasciculus. This combination of factors largely suffices to explain von Monakow's interpretation of the degenerative picture in his case. It seems to me, however, that he has by this very instance furnished a most convincing demonstration of the existence of Wernicke's bundle. It is because von Monakow's case closely resembles ours, particularly with regard to the occasional development of an extreme sagittal layer of association fibres, that we have thought it useful to insert right here this extrinsic discussion.

The next section (Pl. I, Fig. 2) is one through the anterior part of the splenium of the corpus callosum, near the point where it lodges anteriorly the body of the fornix. The splenium shows a very considerable degeneration of its central portion. The descending horn of the lateral ventricle is appreciably dilated. The lesion has already retroceded in great part and is now confined to the edges of the Sylvian fissure, destroying the superior border of the first temporal convolution in the depth of the fissure, and the outermost segment of the inferior border of the supramarginal gyrus. Very small foci of softening may be seen in the subcortex of the paracentral lobule. There is no longer any actual implication of the deep sagittal layers. The tapetum is very thin and greatly degenerated along the lateral ventricular wall. The corona radiata of the parietal lobe is easily distinguishable, and microscopically, it may be seen to send many fibres to, or else receive the same from, the paracentral lobule. Corresponding to the temporal lobe, three strata can be differentiated outside the ventricular wall: the tapetum, the internal and the external sagittal layers. A point especially worthy of consideration, and one upon which I have previously laid much stress is, that opposite the deep substance of the first temporal convolution, there occurs a gradual transposition of the constituent fibres of both sagittal layers; that is to say, the fibres of the external sagittal stratum are pressed inward towards the ventricular wall and crowded against the lower pole and lateral border of the sphenoidal prolongation of the caudate nucleus, while the fibres of the internal sagittal layer pass outward and above the former, occupying both the external and internal sagittal layers. This interchange of domain is a slow but steadily progressive one, beginning posteriorly at a point which corresponds approximately to the termination of the fissure of Sylvius, and continuing as far forward as the level of the pulvinar of the optic thalamus. There

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is no section in my possession which illustrates this point as clearly as that actually under consideration. We note, between the ventricular wall and the bottom of the Sylvian fissure, a broad zone of degeneration which occupies, above, the territory of both the external and internal sagittal layers; it then extends obliquely downward and outward, encroaching less and less upon the internal and occupying more and more the external sagittal layer, until it reaches a point opposite the parallel fissure, where it is seen to cross obliquely the thickness of the external sagittal layer, normal at this point, and to wend its way towards the internal layer. Bearing in mind the extent of the lesion in the occipital lobe, it is evident that this broad degenerated band contains, before all, the thalamic radiations which have been intercepted in their course from the calcarine and other areas of the occipital cortex to the optic thalamus. Only a small proportion of geniculo-calcarine fibres have been severed, and even retrograde degeneration could not account for the marked degenerative sclerosis observed at this point in the external sagittal layer. Moreover, it must be stated that the case is not one of long standing, and not one, therefore, likely to determine a very appreciable degree of retrograde degeneration. Furthermore, as we shall see later, this degenerated area disappears about the pulvinar and dorsal nucleus of the optic thalamus, the anterior corpus quadrigeminum and the internal geniculate body. No appreciable degeneration can be followed to the external geniculate body, nor is this nucleus the seat of any atrophy. I have always maintained that the external sagittal layer of the temporal lobe differs materially from that of the occipital lobe, and that it is erroneous to look upon the external sagittal layer throughout, as a structure of unvarying character, as an anatomo-physiologic entity. This section clearly demonstrates that in the temporal lobe the external sagittal layer contains something else besides the geniculo-calcarine fibres. We have just seen that it harbors the migrating occipital radiations; in addition, it receives fibres derived from the first temporal convolution and coursing to the optic thalamus and internal geniculate body. I believe that it likewise contains fibres which take their origin from the basal ganglia and go to the mesial cortex of the temporal lobe, more particularly to the gyrus hippocampus. The very particular transposition which takes place between the thalamic radiations and the fibres of the external sagittal layer appears to me to be a most logical process; as they approach their end nuclei (pulvinar and anterior corpus quadrigeminum), these cortical radiations take the shortest route and assume the disposition which will ensure free irradiation into them, crowding back temporarily, so to speak, the other fibres whose connections are situated at more anterior levels.

The following section (Pl. I, Fig. 3) passes through the most posterior portion of the superior frontal convolution, the ascending frontal and parietal convolutions, the middle portion of the temporal lobe, the anterior corpus quadrigeminum, the optic thalamus, the internal geniculate body, the posterior capsule of the external geniculate body, the retrolenticular segment of the internal capsule and the body and sphenoidal horn of the lateral ventricle. Small patches of encephalomalacia are

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again observed in the cortex and subcortex of the superior border of the hemisphere, involving the base of the superior frontal convolution and having determined an appreciable pallor of the corona radiata and of the deep substance of the supra-Sylvian convolution (projection and association fibres). At this level, the temporal lobe appears normal save for the presence of areas of degeneration. The deep substance of the first temporal convolution is appreciably degenerated owing to the interruption, in more posteriorly situated regions, of the association fibres which terminate in its cortex. The lower part of the retrolenticular segment and the sublenticular segment of the internal capsule show a very decided degree of degenerative sclerosis. It is seen that this degenerated area forks when it reaches Wernicke's field, one division containing the radiations of the destroyed parietal convolutions continuing upward outside the lamina medullaris externa of the optic thalamus to terminate in the dorsal nucleus of this body; the other containing the radiations of the first temporal convolution passing horizontally inward through the superior portion of Wernicke's field, above and behind the external geniculate body, to finally irradiate into the substance of the internal geniculate body, which shows a very appreciable degree of discoloration and atrophy. Likewise to be noted, is the discoloration more particularly of the middle layer of the anterior corpus quadrigeminum, resulting from involvement of the radiations derived from the visual area.

Case II. Can.... (Pl. II and III).

Extensive patch of softening from obliteration of the left Sylvian artery. The lesion, one of long standing, destroys the deep substance of the Sylvian border of the base of the ascending parietal convolution, the inferior gyri of the island of Reil, practically the whole of the supramarginal gyrus, the most anterior portion of the angular gyrus, the greater part of the first temporal convolution and its accessory superior Sylvian lobule (*circonvolution temporale profonde* of Déjerine) and the deep substance of the posterior two-thirds of the second temporal convolution. A small focus of softening is also found in the deep substance of the anterior extremity of the gyrus hippocampus. A section taken at the level of the descending horn of the lateral ventricle (Pl. II, Fig. 3) shows that the lesion has peculiarly respected, in great part, the cortex, but widely destroyed the white matter, dipping down at several points practically to the lateral ventricular wall and severing along almost its entire vertical extent the deep sagittal layers, save at the infero-external angle. Corresponding to the middle portion of the ventricular wall, it will be seen that although the softening does not extend as deeply at this point, there remains but a sclerotic area absolutely devoid of medullated fibres, as this very territory is itself involved at slightly posterior levels.

The first section (Pl. II, Fig. 1) is taken from the posterior part of the occipital lobe. This lobe, it will be remembered, is absolutely free from lesion. At once it is seen that the degenerative sclerosis is strictly confined to the domain of the external sagittal layer. Close inspection will show that it forms practically a complete ring, although evidently very irregular in contour, having somewhat the shape of the letter L, enclosing

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the tapetum and optic radiation which at this point are normal. The section passes immediately behind the tip of the occipital horn, which in this case is prematurely closed, so that the apposed ventricular walls simply form a vertical septum upon which border, on either side, the tapetum, the internal and external sagittal layers. The tapetum in the actual section may be recognized as a deeply-staining line extending vertically through the middle of the area marked out by the degenerated band. On either side of it a broader and less deeply-stained layer can be made out which represents the optic radiation of cortical derivation; it is especially distinct along the lateral margin of the vertical segment and in the short transverse inferior segment of the field under consideration. The external sagittal layer is so sharply isolated as the result of secondary degeneration that it would seem to have been traced with the point of a pin. It is constituted essentially by the fibres of the geniculo-calcarine fasciculus, which at more anterior levels have been practically totally wiped out by the softening above described. This section shows that in the occipital lobe, these fibres are much more abundant in the ventral segment of the external sagittal layer than in its dorsal segment, which can be seen to consist of a mere line, describing a sort of conic figure as it caps over the tapetum and then descends along its mesial aspect and just without the stratum calcarinum previous to its irradiation into the cortex of the cuneate lip of the calcarine fissure. I have had occasion several times to observe a massive degeneration of either the ventral or dorsal segment of the occipital external sagittal layer, but this is the first time that I see this layer degenerated in its entirety in an otherwise perfectly healthy occipital lobe.

The following section (Pl. II, Fig. 2) passes through a more anterior part of the occipital lobe. Symphysis of the occipital horn here again obtains, but the formation of the forceps major of the corpus callosum lodged in the deep substance of the cuneus is plainly visible. Its continuation inferiorly as the tapetum is still to be distinguished owing to its deeply-staining reaction, and appears as a dark line extending at first vertically downward, then curving mesially beneath the bottom of the calcarine fissure and penetrating into the depth of the lingual lobule. To its outer side, and within the outermost completely degenerated band, the internal sagittal layer of cortical radiations can be made out; it is diffusely degenerated owing to the influence of retrograde changes as we are nearing the seat of lesion. Finally, we observe again the extreme sclerosis of the external sagittal layer (geniculo-calcarine fasciculus), which is almost as sharply defined as in the preceding section. Yet, it is to be noted, that both the superior and inferior transverse segments of this sclerotic band are not strictly confined to the domain of the external layer. Above, the degenerated fibres are seen to closely invest the forceps major, passing therefore through the internal sagittal layer; below, the broad degenerated band of geniculo-calcarine fibres destined to the lingual lobule is interrupted, so to speak, at two points, by normal fasciculi. The more lateral one contains but a small number of fibres and truly belongs to the geniculo-calcarine tract; it has simply escaped involvement in its long course through a partly softened, partly sclerotic

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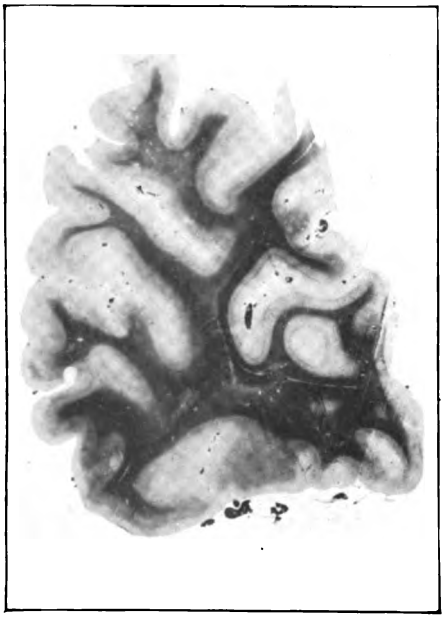
PLATE II



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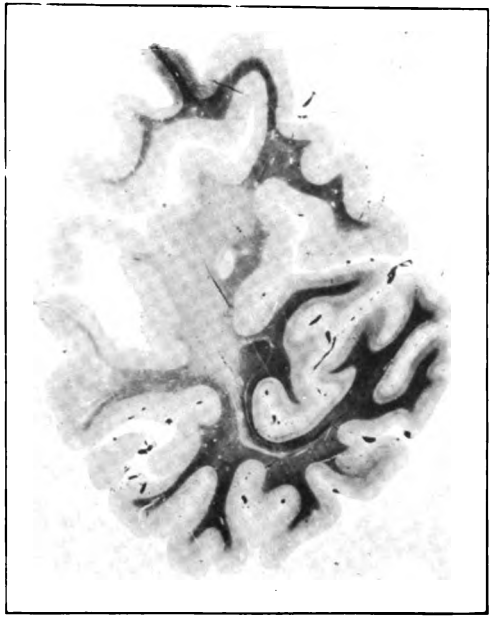

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territory. The more mesially situated healthy fasciculus is much more considerable and does not belong to the geniculo-calcarine tract, but is formed of cortical optic radiations. Careful study will show, indeed, that to the inner side of the lateral normal fasciculus, the degenerated line no longer follows the external layer, but sinks into the internal layer close to lingual segment of the tapetum, and through this channel irradiates into the lower lip of the calcarine fissure, the deep substance of which may be seen to be appreciably degenerated in consequence. So that, if it may be said that the lateral or vertical segment of the occipital external sagittal layer is constituted essentially by corticipetal fibres, or more accurately, by the geniculo-calcarine fibres, differing thus very materially from the corresponding segment of the internal sagittal layer which contains before all corticifugal fibres, or the thalamic radiations of the occipital cortex, the same differentiation cannot be made with regard to the dorsal and ventral mesially-directed segments of these layers. The fibres of the geniculo-calcarine tract situated at both the superior and inferior angles of the lateral segment of the external sagittal layer, in order to reach their field of irradiation, i. e., the cortex bordering upon the calcarine fissure, naturally follow the shortest course which is via the internal sagittal layer. They necessarily mingle with the optic radiations and even crowd the latter aside on arriving close to their point of arborization, so that in the depth of the cuneate and lingual lobules, the internal layer is occupied more particularly by the terminating than by the originating fibres. This feature, moreover, is the rule throughout the cerebro-spinal axis. We have already seen a similar disposition at the level of the optic pulvinar between the terminating thalamic radiations and the emerging geniculo-calcarine fibres.

The pallor of the deep substance of the lateral convolutions, more particularly of the angular gyrus and second occipital convolution, is due, in great part, to the interruption at slightly anterior levels of a large number of association fibres. The peculiar cribriform appearance of the subcortex of the second occipital convolution is a common finding, in my experience, in regions which are themselves intact but which have been long deprived of their afferent medullated fibre-systems. Microscopically, Wernicke's vertical occipital bundle is clearly demonstrable opposite the second and third occipital convolutions, and the same may be said of Sachs's *fasciculus proprius cunei* which is plainly appreciable even in this figure; the mesially-directed dorsal segment of the degenerated geniculo-calcarine tract separating it from the forceps major of the corpus callosum.

The next section (Pl. II, Fig. 3) has already been considered in the general description of the lesion of this case. There is complete destruction of the supramarginal gyrus and first temporal convolution and extensive undermining of the second temporal convolution. At the infero-external angle of the ventricle, the deep sagittal layers can be plainly recognized and ascend for a very short distance along the lateral ventricular wall, terminating above in a field, which, although bordering directly upon a cavitary focus, contains a fair number of well-stained fibres which have peculiarly escaped destruction. This island of healthy

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fibres belongs, in great part, to the geniculo-calcarine tract and is identical with the normal lateral fasciculus described in the preceding section in connection with the external sagittal layer. Below this field, the sagittal layers are totally degenerated and seem continuous with the equally totally degenerated subventricular segment of the internal sagittal layer. Microscopically, it is seen that this sclerosis extends mesially into the depth of the gyrus hippocampus; so that it may be safely assumed that at this level, the external sagittal layer contains a certain number of fibres which go to the mesial convolutions of the temporal lobe *via* the subventricular segment of the internal sagittal layer. The corresponding segment of the external sagittal layer is relatively normal and well-developed; we are of the opinion that in this region there enters into its formation, aside from the geniculo-calcarine tract, a large number of fibres derived from the mesial convolutions, more particularly from the gyrus hippocampus. A certain proportion of these may perhaps follow an inverse course, going to the same region from the basal ganglia.

A section taken at the level of the pulvinar of the optic thalamus (Pl. III, Fig. 4) shows the extreme discoloration and atrophy of this body, resulting from interruption of the great majority of the occipital radiations. The anterior corpus quadrigeminum being connected with the thalamus at this point, it is readily seen that the secondary degenerative sclerosis traverses the entire breadth of the pulvinar passing directly into the superficial and middle zones of the colliculus, and that it may even be followed into the quadrigeminal commissure as far as the mesial line. The only region of the pulvinar which contains normal-staining fibres is that situated at its infero-external angle; it corresponds to the external retro-geniculate area and forms the lower part of what is classically known as the triangular field of Wernicke. The fibres which constitute this normal area take their origin, for the most part, from the external geniculate body. The remaining mesial segment of the lower border corresponds to the internal retro-geniculate field; it is exceptionally degenerated and shrunken as it receives the cortical radiations of the first temporal convolution, which, as we have already seen, is destroyed in the greater part of its extent. The lesion at this point involves the Sylvian border of the ascending parietal convolution, spares the contiguous portion of the island of Reil but undermines its temporal portion, completely destroys the first temporal convolution and sinks into the deep substance of the second temporal, whence it extends more deeply at one point and completely severs the external and internal sagittal layers. The latter focus exactly replaces in this section the sclerotic field observed in the previous section at the infero-external angle of the sphenoidal horn. The normal fibres which then lay immediately above it are now seen to trend mesially towards the lower pole and lateral border of the sphenoidal prolongation of the caudate nucleus. These fibres, it will be remembered, we attribute to the geniculo-calcarine fasciculus. Below the seat of lesion, the external sagittal layer appears diffusely degenerated owing to the presence, at more anterior levels, of additional linear extensions from the main area of softening. The tapetum and internal sagittal layer are likewise appreciably degenerated. The intense degeneration of the retro-

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PLATE III

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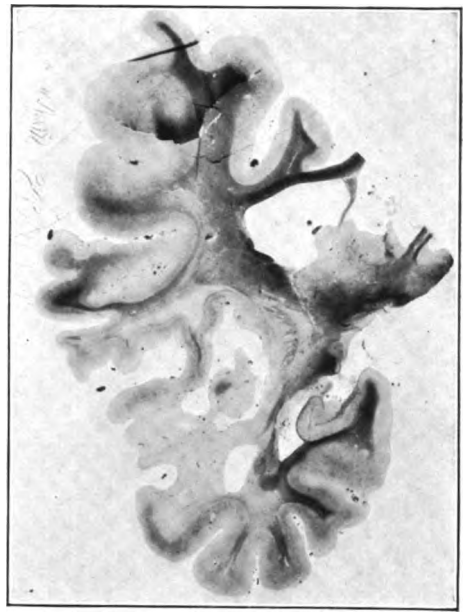

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and sublenticular segments of the internal capsule is fully explained by the interruption of all the cortical radiations derived from the occipital lobe, the first and second temporal convolutions, the insular region and the supra-Sylvian gyri. Retrograde degeneration of the internal and external geniculate fibres undoubtedly contributes its share towards rendering this sclerosis so extreme. Without the sagittal layers, the marked discoloration of the deep substance of uninvolved convolutions reveals the widespread connections of the association fibre-systems, the interdependence of supposedly distinct association tracts. In the temporal lobe, the pallor of the subcortex extends beneath the sphenoidal horn into the depth of the gyrus hippocampus, thus showing that the inferior segment of the cingulum reacts to lesions of the lateral convexity. This involvement of the cingulum serves at the same time to delimit the subventricular segment of the external sagittal layer, a projection-path with which it is so intimately blended in the normal state that it is impossible to distinguish between them. This very intimacy of relationship has unquestionably been a most potent factor in inducing the earlier writers to regard the ventral portion of the external sagittal layer as an association bundle. In the parietal lobe, likewise, the degeneration of the fasciculus arcuatus extends high up into the ascending frontal convolution, sharply defining the base of the corona radiata against the short subcortical association-loops. The degeneration even affects the fronto-parietal or superior segment of the cingulum, and despite the unfortunate tear in the upper part of the section, the pallor of the deep substance of the gyrus fornicatus is distinctly appreciable. There exists a considerable atrophy of the body of the corpus callosum and of the fornix. A last feature of interest is the sharpness of outline of the anterior and posterior brachia of the quadrigeminal bodies resulting from the extreme discoloration of the superficial and middle layers of the anterior colliculus.

The following section (Pl. III, Fig. 5) passes through the most posterior portion of the external geniculate body which is seen to be decidedly atrophied, shrunken and discolored, especially in its mesial segment, as the result partly of retrograde degeneration and partly of prolonged functional inactivity. Nevertheless, the lateral limiting field of Wernicke is abundantly supplied with healthy nerve-fibres except in its superior portion, where it is traversed by the dorsal fasciculi of the geniculo-calcarine tract in their course from the geniculate body to the vertical segment of the external sagittal layer. That these bundles have undergone retrograde degeneration, there can be no doubt. Their course through the retrolenticular segment of the internal capsule is easily followed. Immediately beneath this degenerated zone, several obliquely-directed healthy fasciculi are seen to abandon the external sagittal layer and to wend their way mesially and upward towards Wernicke's field; they are the very fibres which, in the preceding section, were seen to collect about the caudate nucleus. They have simply been displaced upwards in their forward course and pass gradually into the lowermost field of the internal capsule. Similarly, it will be noticed that the next lower segment of the external sagittal layer, previously occupied by a focus of softening, now a thoroughly sclerotic area, tapers down to a fine

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filiform process as it passes upward and inserts itself between the caudate nucleus and the overlying healthy fasciculi, which it thus displaces upward and laterally towards the external capsule and into the retrolenticular division of the internal capsule. This section, I consider admirably suited, owing to this rare alternation of preserved and degenerated fasciculi of geniculo-calcarine fibres, to demonstrate the peculiar détours which these fibres follow in reaching the external sagittal layer after their emergence from the external geniculate body. All these features were incorporated, however, in my first description of the geniculo-calcarine tract. A fact to be noted, is that the healthy fasciculi coursing towards Wernicke's field comprise a larger number of fibres than the sum total of the fibres which escaped involvement and which form the normal field observed at the infero-external angle of the sphenoidal horn. This reappearance of normal-staining medullated fibres in the domain of the retro- and sublenticular segments of the internal capsule steadily increases as we consider more and more anterior levels, and this fact, coupled with the existence of a fairly well-supplied field of Wernicke, clearly shows that there is a partial restoration of the degenerated geniculo-calcarine tract before it reaches its nucleus of origin, the external geniculate body. In other words, ascending, cellulipetal or retrograde degeneration has not extended over the entire length of the central segment of the divided nerve, but has become arrested at a variable distance from its trophic centre. The linear degeneration of the remainder of the external sagittal layer has become more distinct. The degeneration of the internal sagittal layer is well-marked and involves more particularly the constituent fibres of Türck's fasciculus, of which that layer at this level is largely composed. The retrolenticular segment of the internal capsule is less widely degenerated than in the preceding section but the sclerosis is more intense. The fronto-parietal corona radiata which was previously relatively well-preserved, now presents an appreciable degeneration more especially of its lateral field (*stratum sagittale externum fronto-parietale* of Anton and Zingerle); its mesial division, on the contrary, remains practically normal. This latter segment of the fronto-parietal corona radiata has received several names: "corona radiata of the caudate nucleus" (Meynert); "callosal fasciculus coursing to the internal capsule" (Wernicke, Gratiolet, Foville); "reticular zone of the corona radiata" (Sachs); "stratum sagittale internum" (Anton and Zingerle). This last designation appears to us to be the most appropriate for this layer which contains fibres belonging to both projection and commissural systems. The commissural fibres are fewer in number, pursue a vertical course (on a frontal section) and simply represent the callosal radiations going to and from the island of Reil and the first temporal convolution; so that the predominating and therefore distinctive element of the fronto-parietal internal sagittal layer is the projection-fibre. Sachs has always maintained this view and demonstrative cases have been published by Anton-Zingerle[5] and by me[6]. It is

[5] Anton Zingerle: Bau, Leistung und Erkrankung des menschlichen Stirnhirnes, pp 155–160, Graz 1902.

[6] Nouvelle Iconographie de La Salpêtrière, 1906, No. 2, pp. 200–201.

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this very structure, it will be remembered, which Déjerine and others have attempted to isolate as a long association tract "the occipito-frontal fasciculus." If such were the true nature of the internal layer of the fronto-parietal corona radiata, I should certainly expect to find it appreciably compromised in this case in which there is complete destruction of the deep sagittal layers bordering upon the lateral wall of the descending horn of the lateral ventricle and interruption therefore of the great majority of the fibres of occipital derivation. On the contrary, we find it remarkably intact. It remains so throughout the series of sections, despite the fact that for some considerable distance anterior to the actual level, the supra-Sylvian convolution continues to be the seat of lesions which encroach upon the proximal field of the corona radiata and which have determined a marked degeneration of the entire posterior limb of the internal capsule. It thus becomes evident that the internal sagittal layer differs materially from the external layer as regards the source and connections of its constituent fibres. I have already expressed the opinion that this layer is in relation with the mesial surface of the fronto-parietal lobe, more particularly with the gyrus fornicatus, and that its fibres are mainly corticipetal, taking their origin probably from the anterior tubercle and mesial nucleus of the optic thalamus. There is an appreciable discoloration and atrophy of the dorsal half of the optic thalamus, most marked in the region of the lateral nucleus which is in relation with the parietal lobe. The mesial segment of the thalamus is likewise rather pallid, but it is normally poor in medullated nerve-fibres. Lying directly upon its ventricular surface is seen the ganglion habenulae with its ascending fasciculus, the taenia thalami. The posterior commissure appears very distinctly subdivided into two bundles, of which the superior represents the stem of the pineal gland. The internal geniculate body is markedly atrophic and flattened from above downward; its ventral segment is totally empty, whereas its dorsal segment receives the terminating fibres of the posterior brachium which may also be followed microscopically into the dorsal laminae of the external geniculate body. The degeneration of the parietal and temporal divisions of the cingulum is still distinctly appreciable.

The next section (Pl. III, Fig. 6) differs but very little from the foregoing from which it is separated by only three serial numbers. It is mainly intended to show the appearance of the external geniculate body at the level of its full development. It will be seen that this body has preserved its gross morphology, but that it is decidedly atrophic generally and that its transverse diameter particularly is much reduced. On closer study, it appears, so to speak, bisected in its vertical extent; its mesial segment, totally discolored, is more slender, shorter and does not appose itself fully to the outer segment, but seems displaced upwards. The lateral segment presents the typical laminated arrangement and is limited externally by the triangular field of Wernicke which is rapidly gaining in number of medullated nerve-fibres. The sublenticular division of the internal capsule is likewise more abundantly supplied. The aspect of the external geniculate body is typical and there can be no doubt that in the production of this marked discoloration and atrophy, retrograde degener-

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ation has been chiefly concerned; but it must not be forgotten that the softening is one of old date and that the geniculo-calcarine tract has been intercepted at a relatively proximal distance from its nucleus of origin, much nearer the external geniculate body than the calcarine cortex. We have thus present the two main elements which determine retrograde degeneration, chronicity and proximity of lesion. This appearance is rare, I believe, in lesions even of long standing limited to the occipital lobe. I have often seen under such circumstances, a generalized atrophy of the external geniculate body but without appreciable concomitant discoloration; the proximal portion of the geniculo-calcarine tract would be reconstituted in front of the lesion though it would likewise present a distinct atrophy. The atrophy of both the geniculate body and its tract, I attribute to the unquestionable influence of functional inactivity.

Case III. Col.... (Pl. IV,).

Central softening of the right temporal lobe from obliteration of the sphenoid branch of the middle cerebral artery. The lesion, one of only four weeks' standing, extends from the tip of the temporal pole in front to about the level of the anterior border of the splenium of the corpus callosum behind. The patch is irregularly pyramidal in shape, with its base directed forward and its apex inserted in the tapetum of the descending horn of the lateral ventricle below the point where the caudate nucleus curves forward to pass into the sphenoidal horn. The lesion spares at all points the cortex and the immediate subcortical zone. Anteriorly, at the level of the anterior border of the external geniculate body (Fig. 1), the softening destroys all the deep white matter situated to the outer side of the sphenoidal horn, i. e., the deep substance of the three temporal convolutions and the fusiform lobule; it spares entirely the gyrus hippocampus. It is limited above by the lenticular nucleus which is itself totally undisturbed, internally by the ventricular wall, below and to the outer side by the subcortex of the temporal convolutions. The destruction has been so extreme that a cavity with jagged walls is all that remains of the centrum of this region. The occipital lobe is absolutely intact.

This case, like the others, has been studied by means of serial sections from the temporal to the occipital pole. The temporo-parietal sections have been stained according to the Weigert-Pal method; the entire occipital lobe has been subjected to osmic acid impregnation.

A section taken at the level of the full development of the external geniculate body (Pl. IV, Fig. 1) shows that all that remains of the white matter of the temporal lobe is the subcortical system of short association fibres. These fibres stain relatively well and the Baillarger streak is noticeably well-preserved in the cortex of the first temporal convolution. The external geniculate body has retained its normal configuration but appears atrophic, it is shrivelled up generally and flattened from side to side; its myelin-lamellae though well-stained are pressed closer together and present numerous angular deflections. At more posterior levels, the inner segment of the external geniculate body is not only atrophied but even discolored and no longer apposes itself fully to the outer segment, thus producing the peculiar bisected appearance al-

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ready observed in the preceding case. Nevertheless, in this as in all other sections passing through the external geniculate body, it is seen that Wernicke's field is unusually well-supplied with normal-staining medullated fibres. From the upper part of Wernicke's field a considerable number of them can be followed outward into the peri-focal sclerotic zone; they represent, for the most part, geniculo-calcarine fibres which have not yet undergone retrograde degeneration. The lower part of Wernicke's field, however, is occupied by several decidedly degenerated fasciculi which belong to Arnold's temporo-thalamic bundle, the fibres of which course from the temporal pole to the optic pulvinar. At slightly anterior levels, a fairly broad and totally sclerosed fasciculus can be followed from the sublenticular segment of the internal capsule, above the external geniculate body and the optic tract, into the outermost division of the pes pedunculi; it represents Türck's temporo-cerebellar tract. In the actual section the lower field of the posterior limb of the internal capsule is diffusely but distinctly degenerated. The external and extreme capsules are markedly degenerated and the discoloration may be followed upward into the subcortex of the parietal convolutions as high as the superior hemispheral border. Beneath the sphenoidal horn, the transverse segment of the external sagittal layer is partly preserved, but it consists at this level especially of the fibres of the cingulum and its relative integrity may be explained by the fact that the gyrus hippocampus is intact. Below this layer the subcortex is decidedly discolored and the degeneration extends very distinctly into the most mesial portion of the gyrus hippocampus where it occupies the domain of the cingulum. The corresponding portion of the tapetum contains a few deeply-stained fasciculi which seem to emerge from the hippocampal septum and which advance beyond the infero-external ventricular angle.

The internal sagittal layer of the fronto-parietal corona radiata is practically intact and in this particular series of sections appears unusually well-defined. It will be noticed, however, that the adjacent subependymal zone is distinctly degenerated, and that the discoloration extends into the hook-shaped peri-ventricular portion of the corpus callosum and then mesially along the lower border of the callosal commissure; showing that anterior temporal lesions react upon the trunk of the corpus callosum. An appreciable degeneration is observed in the mass of fibres (dorsal thalamic bundle) which course along the superior border of the optic thalamus and join the contiguous portion of the internal capsule. The area of degeneration extends downward outside the lamina medullaris externa of the optic thalamus and is probably related to the lesion of the fibres derived from the hippocampal and uncinate gyri. I have previously referred to the fact that important connections are established between the optic thalamus and the gyrus fornicatus, or first limbic convolution, through the dorsal thalamic bundle and the internal sagittal layer of the fronto-parietal corona radiata; it is possible that this bundle serves to establish similar connections with the gyrus hippocampus, or second limbic convolution, by means of fibres which traverse the temporal corona radiata and the internal capsule. A very distinct pallor

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is noticeable in the domain of the internal geniculate body and in the deep portion of the anterior corpus quadrigeminum.

The sections intervening between this one and that next to be described show a very decided atrophy and discoloration of the mesial segment of the optic thalamus which we know to be in relation with the temporal convolutions. The area of softening becomes more and more circumscribed, abandons the subcortex of the first temporal convolution and recedes from the lower hemispheral border, forming a quadrangular focus limited to the deep sagittal layers which border upon the lateral ventricular wall. The posterior and retrolenticular segments of the internal capsule appear diffusely degenerated throughout the series of sections, and this degeneration, which is too widely distributed to correspond exclusively to the passage of the temporal cortical radiations into the optic thalamus, evidently represents in part the temporal fibres which reach the corpus callosum via the external and internal capsules.

A section passing through the splenium of the corpus callosum (Pl. IV, Fig. 2) shows that the lesion is now confined to that portion of the tapetum and internal sagittal layer situated immediately beneath the descending segment of the caudate nucleus. A distinct degeneration is observed in the central portion of the splenium and extends upward along the lower segment of the forceps major. The internal sagittal layer of the parietal corona radiata is still readily discernible and apparently normal. In the temporal lobe, the external sagittal layer has become reconstituted practically in its entirety, whereas the internal sagittal layer is massively degenerated, appearing as an exceptionally well-defined sclerotic band which courses mesially below the sphenoidal horn and disappears in the depth of the gyrus hippocampus where it blends with the area of degeneration of the cingulum. The ventral portion of the tapetum like the external sagittal layer is in good part restored, but peculiarly enough, both these structures are far less preserved than would appear from the macroscope study of this section and from comparison with the markedly discolored internal sagittal layer. Microscopically, it is seen that the external sagittal layer, its ventral segment more particularly, contains but few normal fibres. For the most part, the fibres are coarsely fragmented or reduced to irregularly beaded shreds, and the whole layer is stuffed with granular bodies. That such an altered fibre-mass should still exhibit relatively good staining qualities would seem at the first glance difficult to explain; but it must not be forgotten that we have to do with a softening of only four weeks' duration, which is hardly sufficient to determine a sclerosis appreciable with the Weigert-Pal method. The fact that other tracts, the internal sagittal layer, for instance, already show distinct discoloration, is not contradictory of the above statement. We know that normally, the various tracts differ very considerably in their susceptibilities to staining reagents as regards both rapidity and intensity of reaction; likewise, we know that pathologically, there are appreciable variations in the degree of resistance offered by the individual tracts to degenerative sclerosis.

Here again, outside the vertical segment of the external sagittal layer a well-defined zone of discoloratior exists, which can be followed upward

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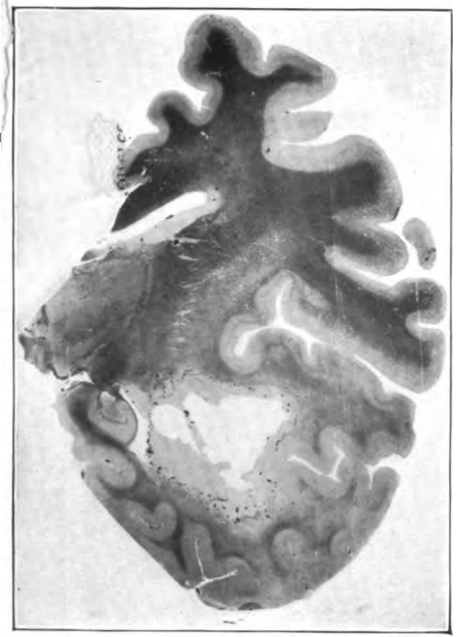
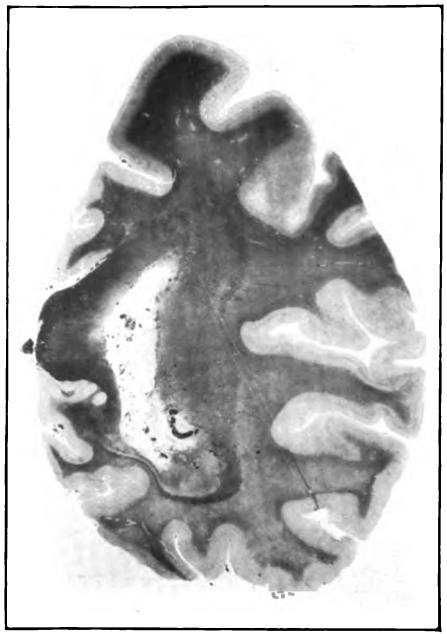
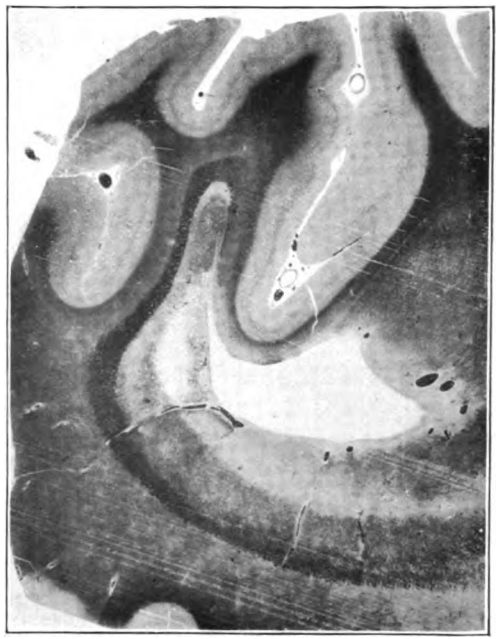
PLATE IV



1



2



3

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into the subcortex of the parietal convolutions and mesially beneath the sphenoidal horn into the depth of the gyrus hippocampus; showing that the cingulum derives a fair proportion of its constituent fibres from the convolutions of the temporal convexity. It should be stated that at this level, the domain of the geniculo-calcarine fasciculus is actually occupied in great part by the focus of softening and that the corticifugal projection fibres derived from the mesial convolutions and inferior border of the temporal lobe course through the external sagittal layer; a fact which contributes materially to the relative staining integrity of this layer.

The Marchi sections through the occipital lobe (Pl. IV, Fig. 3) all show abundant granular bodies. In the anterior portion of this lobe, the granular bodies occupy mainly the ventral segment of the external sagittal layer and the corresponding portion of the tapetum; the internal sagittal layer being practically free. As we consider more and more posterior levels, we note that the Marchi granules gradually ascend through the vertical segment of the external sagittal layer until we reach the occipital pole, when it is seen that they have invaded the whole of the external layer, forming practically a closed ring of granular bodies around the internal sagittal layer and the retroventricular callosal stratum. Throughout the posterior portion of the occipital lobe, the granules are essentially confined to the domain of the external layer, which they thickly beset throughout; but they are far more abundant in its ventral than in its dorsal segment. The tapetum and internal sagittal layer contain at this level but few granular bodies. Outside of the external sagittal layer and corresponding to the subcortex of the occipital convexity, a few stray granules are here and there to be seen, which evidently represent degenerated association fibres derived from the temporal lobe. From the superior and inferior horizontally-directed segments of the external sagittal layer, strings of granules are constantly detached which radiate into all parts of the cortex bordering upon the calcarine fissure. In many places the granules may be followed beneath the Gennari line. In their course from the external sagittal layer to the calcarine cortex, the degenerated fibres pass, in considerable numbers, through the internal sagittal layer.

RÉSUMÉ AND INTERPRETATION OF THE VARIOUS DEGENERATIVE SCLEROSES AND NUCLEAR ATROPHIES OBSERVED IN ALL THREE CASES.

In the first place as regards the external sagittal layer, we have seen that its occipital portion degenerates from before backward in cases of deep-seated lesions of the temporal lobe. Twice, once with the Weigert-Pal stain and once with the Marchi method, we have found a complete sclerosis of the external sagittal layer in an otherwise perfectly healthy occipital lobe, induced by extensive foci of encephalomalacia limited to the temporal lobe. We must therefore assume that the course of the constituent fibres

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of the occipital external sagittal layer is corticipetal. In Case I, in which the softening is confined to the posterior part of the parieto-temporal lobe, we have seen that in the more anterior and normal regions of the temporal lobe, the degenerative sclerosis occupies both the external and internal sagittal layers, but that it is far less voluminous than would be expected from the extensive lesion of the peri-Sylvian convolutions; showing that a fair proportion of the fibres intercepted have become reconstituted in front of the lesion, *i. e.*, that their course must therefore be corticipetal. Under both groups of circumstances then, we have very distinct evidence that the constituent fibres of the occipital external sagittal layer take their origin from some level anterior to that of the pulvinar of the optic thalamus. The actual cases do not permit us to make more definite statements regarding the real source of these fibres, but we have previously demonstrated that anterior temporal lesions limited to the cortex and immediate subcortex determine no appreciable reaction in the domain of the occipital external sagittal layer and that the external geniculate body represents the nucleus of origin of this layer.

We have already sufficiently insisted upon the fact that the external sagittal layer of the temporal lobe is a far more complex structure than that of the occipital lobe and that it is grossly incorrect to regard the one as the unmodified continuation of the other.

The intimacy of relation between projection and association fibres has been a constant feature throughout. Particularly instructive in Case I in which it furnished the motive for comparison of our case with that of von Monakow, this feature was likewise distinctly appreciable in both the other cases. Owing to secondary degeneration, the domain of the external sagittal layer, which, in the normal state, is extremely ill-defined against that of the cingulum in the temporal lobe and that of the bundles of Sachs, Vialet and Wernicke in the occipital lobe, became sharply delimited. The interdependence of the various association tracts is another feature which this series of cases serves to clearly demonstrate. We saw that both divisions of the cingulum, the parietal which courses through the subcortex of the gyrus fornicatus and the temporal which occupies the depth of the gyrus hippocampus, were decidedly affected by lesions of the temporo-parietal convexity; Cases II and III both illustrate this point

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very distinctly. The cingulum which is generally regarded as being the great association bundle of the mesial hemispheral region is thus likewise related to the lateral convexity, as it receives from the latter territory a considerable number of fibres. We believe that the parietal segment of the cingulum is in relation with the fasciculus arcuatus and the temporal segment with the fasciculus uncinatus. Again, it was observed in Case III, that the lesion in the domain of the fasciculus uncinatus had determined an appreciable discoloration of the fasciculus arcuatus by means of fibres which course upward through the external capsule. It thus becomes apparent that all the association-tracts of the cerebral hemisphere are more or less interdependent.

The tapetum, *i. e.*, the innermost of the deep sagittal layers of the temporo-occipital lobe, that which borders directly upon the ventricular ependyma, is constituted essentially by the fibres of the corpus callosum of which it is simply the intrahemispheral expansion. It abandons fibres to and receives the same from all the convolutions; these fibres traversing in their course the internal and external sagittal layers more or less at right angles. The callosal radiations of the anterior portion of the temporal lobe reach the trunk of the corpus callosum by coursing through the external and internal capsules; a fact well illustrated in Case III. The external capsule is thus in great part tributary of the callosal system, conveying likewise the callosal fibres of the island of Reil.

The tapetum is totally independent from the internal sagittal layer of the fronto-parietal lobe. The statement of Déjerine and others, that lesions of the temporal lobe react upon this layer, is not borne out by the facts observed in our cases. In both Cases II and III, the greater part of the temporal lobe, including the tapetum, is destroyed, and yet we note the persistence of the fronto-parietal internal sagittal layer which is even exceptionally well-defined. This layer, we repeat, is part and parcel of the corona radiata.

In Cases II and III we observed a massive degeneration of the outer division of the pes pedunculi or ventral segment of the cerebral peduncle. This area, as is well known, is the domain of Türck's fasciculus, the constituent fibres of which are derived from the cerebral cortex and pass into the brain-stem through the sublenticular division of the internal capsule. In Case I, in which

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the lesion is practically confined to the parieto-occipital lobe, involving only the base of the first temporal convolution, there exists no appreciable sclerosis in the domain of the pes pedunculi. The study of these cases shows that the parietal and occipital lobes do not send any fibres into the ventral portion of the brain-stem as was formerly supposed. Türck's fasciculus is derived solely from the cortex of the temporal lobe.

In Cases II and III, in which all connections between the basal ganglia and the calcarine cortex have been destroyed, we note an extreme discoloration and atrophy of the optic pulvinar and anterior corpus quadrigeminum and an atrophy of the external geniculate body. In Case II, owing to retrograde degeneration, this body presents, in addition, a marked discoloration. In all three cases there exists, in keeping with the involvement of the first temporal convolution, a decided atrophy and degeneration of the internal geniculate body; a relation first established by von Monakow and subsequently confirmed by Mahaim, Déjerine and others.

In Cases II and III in which the greater part of the temporal lobe is destroyed, there exists a marked atrophy and degeneration of the mesial nucleus of the optic thalamus; in Cases I and II, in which there is likewise considerable implication of the parietal lobe, we note in addition, a distinct discoloration and atrophy of the dorsal segment of the lateral nucleus.

CONCLUSIONS.

1. The external sagittal layer of the temporo-occipital lobe is composed essentially of projection fibres; its occipital segment is constituted by the geniculo-calcarine fasciculus, the fibres of which take their origin from the external geniculate body and terminate in both the upper and lower lips of the calcarine fissure, but more particularly in the latter.

2. The various association tracts of the cerebral hemisphere are all more or less interdependent and represent topographic subdivisions of one main fibre-system rather than distinct and individual bundles.

3. The tapetum is formed essentially by the fibres of the corpus callosum.

4. The internal sagittal layer of the fronto-parietal lobe is part and parcel of the corresponding portion of the corona radiata and

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probably serves to establish the connections between the gyrus fornicatus and the optic thalamus.

5. Türck's bundle takes its origin exclusively from the cortex of the temporal lobe. The parietal and occipital lobes take no part in the constitution of the pes pedunculi or ventral segment of the cerebral peduncle.

6. The existence in the brain of man of an occipito-frontal association bundle is totally inadmissible.

In terminating, I desire to acknowledge my indebtedness to my teacher, Pierre Marie, who has kindly supplied me with the material utilized for this publication.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX, WITH THE REPORT OF TWO CASES.

By C. W. LOUIS HACKER, M. D.

The present general interest in primary carcinoma of the vermiform appendix, a disease at one time of interest only to the pathologist but now attracting also the attention of the surgeon, appears to warrant the publication of the observations herein detailed. The literature of the subject has been fully covered by recent writers and only a brief summary of it will be given in this report.

Attention was first called to the subject in 1882 by Beger who made a clinical as well as histologic diagnosis. The second case was reported by Stimson in 1896, since when the number has steadily increased. The increase in the number of reported cases is in all probability due to the now almost universal custom of examining microscopically all material removed at operation. I have collected from the literature ninety-five undoubted cases in which a histologic diagnosis was made. These are reported by Burman, Baldauf (3), Barrow, Battle, Becker, Beger, Biggs, Brandt (2), Coons, Cullingworth and Comer, Driessen, Eccles, Elting (2), Giscard, Goffe, Grünbaum, Hammond, Harte (9), Harte and Willson (2), Hurdon, Hessberg, Jessup, Jones and Simmons, Kaufman (2), A. O. J. Kelly (5), Kelly and Hurdon (3), Korte (3), Kudo (4), Landau, LeConte, Lejars, Letulle and Weinberg (8), Lubarsch, Mason and Rhea, McBurney (2),

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McCosh, McWilliams, Moschcowitz (3), Mosse and Daumic, Myerstein, Neri, Norris, Patel, Regling, Rolleston, Schrumpf, Stimson, Walsham, Warthin, Weber, Weinberg, Weir, Weil, White and Zaaijer (6).

Of the above cases, eight were examined at this laboratory. These, reported by Elting, Baldauf and Harte I shall describe briefly.

I. *Elting*—Mrs. L., thirty-six years of age, had shown no symptoms of appendicitis. A bilateral salpingo-oophorectomy was performed for chronic pelvic inflammation. The appendix, apparently normal, was removed, as a matter of routine, but on microscopic examination was found to be the seat of a small alveolar carcinoma, one cubic centimeter from the proximal end. The lumen was everywhere obliterated.

II. *Elting*—The patient was a male, eighty-one years of age. The appendix was removed at autopsy on an individual whose death was due to pulmonary tuberculosis and cardiac disease. The clinical history presented no symptoms of disease of the appendix. The appendix was free from adhesions and measures five and five-tenths centimeters in length. The distal portion of the organ for a distance of three and five-tenths centimeters was much enlarged (three centimeters in diameter). Projecting from the convex surface of the enlarged portion at about its middle point and opposite the mesenteric attachment was a mass of yellowish green, translucent gelatinous substance. On section through the middle of the organ the lumen was found to be filled with a similar gelatinous material. Sections showed colloid carcinoma.

III. *Baldauf*—Mr. H., thirty-eight years of age, presented symptoms of appendicitis the day before the operation. The appendix was adherent beneath the umbilicus, and was considerably thickened and covered with fibrin. The lumen was patent and the mucosa injected and the seat of small foci of necrosis. The anatomical diagnosis was acute appendicitis and the microscopic diagnosis carcinoma simplex with ulceration, acute appendicitis and periappendicular suppuration.

IV. *Baldauf*—Mr. B., twenty-three years of age, had had three attacks of appendicitis, the last beginning five years before the operation. The appendix was adherent and the lumen obliterated. Microscopic examination revealed an alveolar carcinoma replacing the mucosa and invading the muscularis and, on the mesenteric side, subserous tissue also.

V. *Baldauf*—A girl, eight years of age, presented symptoms of appendicitis, severe in character, two days before the operation. The appendix was surrounded by an inflammatory mass and contained a small amount of pus in its distal portion which was thickened and indurated and surrounded by granulation tissue. The proximal half was normal and the entire lumen patent. The anatomical diagnosis was chronic appendicitis with partial organization of a periappendicular abscess; the microscopic examination revealed an alveolar carcinoma involving the submucosa.

VI. *Harte*—Miss M. A., fourteen years of age, presented a history of acute appendicitis. The appendix was swollen and measured six and

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five-tenths centimeters in length. The external surface was covered in places by a fibrino-purulent exudate. All coats were thickened and the mucosa presented numerous punctate hemorrhages and small areas of ulceration. At a distance of two cubic centimeters from the proximal end was a slight thickening affecting, particularly, the mucosa. The anatomical diagnosis was acute diffuse and ulcerative appendicitis with fibrino-purulent periappendicitis. The microscopical examination showed an alveolar carcinoma in addition to the acute inflammatory condition.

VII. *Harte*—Miss W. P., thirteen years of age, had a definite history of appendicitis. The appendix was markedly thickened and firmer than normal. To its peritoneal surface were attached numerous firm fibrous tags and one cubic centimeter from the tip was an area of necrosis with perforation. The lumen was patent and the mucosa thickened and studded with minute hemorrhages. An anatomical diagnosis was made of chronic appendicitis with acute exacerbation, gangrene and perforation. The microscopic examination revealed in addition a carcinoma of the appendix.

VIII. *Harte*—Miss K. B., twenty-one years of age, presented a clinical history of appendicitis. The appendix throughout the distal two-thirds was considerably thickened and at the distal extremity had numerous firm tags attached. At the junction of the middle and proximal thirds the lumen was obliterated and the distal end was considerably thickened and filled with a greenish faecal mass. The mucosa of the distal two-thirds showed spots of hemorrhage. Microscopic examination showed in addition to the chronic obliterative appendicitis a primary carcinoma.

In addition to these eight cases observed in this laboratory, I have met with two others during the first year of my service as assistant in surgical pathology. In neither of these was there a history of appendicitis, the appendix in each instance being removed in the course of an operation on other organs. Brief summaries of the clinical histories and pathological examinations follow:

Case I. Records of the Bender Laboratory, Surg. Path. No. 07-557. Clinical History—Mrs. J. M. S., thirty-one years of age, married, entered the Albany Hospital (service of Dr. A. H. Traver) on April 21, 1907. Her family history was uneventful and her past history offered no evidence of disease of the appendix. Since her last menstruation (February 28, 1907) she has had a dull pain in lower abdomen which increased in March and April. Physical examination revealed an old laceration of the perineum and uterine cervix and a purulent discharge from the cervical canal. At the operation on April 22d, the uterine cavity was curetted and the perineum and uterine cervix repaired. On account of a past history of eclampsia a laparotomy was performed to ligate the Fallopian tubes. The right ovary being cystic, a salpingo-oophorectomy was performed. The appendix was removed as a matter of routine. Convalescence was uneventful and the patient has improved in health since the operation.

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Pathological Examination.—The specimen consists of an appendix five cubic centimeters in length. The peritoneal surface is normal. The distal half of the organ is thickened and indurated and twice the diameter of the proximal end, the latter being normal. The lumen is patent throughout and the mucosa normal. Anatomical diagnosis was chronic appendicitis.

Microscopic Examination—The mucosa is intact but between the glands of Lieberkühn occasional small areas of newly formed connective tissue are present. Beneath the mucosa are occasional irregular areas of lymphoid tissue. At one side and entirely within the submucosa are areas of densely packed cells, the outlines of which are indistinct but which are of the epithelial type. The nuclei of these cells are round, deeply staining and show no evidence of mitosis. The smaller areas have a tubular arrangement. No direct communication between these areas and the epithelium lining the glands of Lieberkühn or covering the mucosa, is present. Throughout the submucosa and musculature considerable granulation tissue is present. There is a marked infiltration of leucocytes which at one point in the submucosa form a distinct abscess. The peritoneal coat is oedematous and contains a few leucocytes. The blood vessels are engorged. Microscopic diagnosis—carcinoma simplex of the vermiform appendix. Chronic appendicitis.

Case II. Records of the Bender Laboratory, Surg. Path. No. 07-698. Clinical History—Mrs. M. C., thirty-nine years of age, married, multipara, entered the Albany Hospital (service of Dr. J. A. Sampson) on May 7, 1907. The family history is of little importance. Past history reveals no symptoms suggesting appendicitis. *Present illness*—Ten days before admission to the hospital patient had an acute attack of pain in the lower abdomen associated with fever. No diagnosis was made and the findings at the operation, ten days later, failed to disclose any cause for the symptoms. The diagnosis was made on admission of weakened pelvic floor with retroflexed uterus. At the operation on May 10th a retroflexed uterus was fixed. As a matter of routine the appendix was examined and as a small nodule was felt the appendix was removed. The pelvic floor was then repaired. The convalescence was uneventful. The patient has been in excellent health since the operation.

Pathological Examination. Specimen consists of an appendix measuring six centimeters in length and having a mesentery attached. About five millimeters from the tip it is bent upon itself beyond which is a constriction due to a fibrous band passing around it. Between the distal end and the mesentery a distinct band of adhesions is present. At the junction of the middle and distal thirds is another constriction. The blood vessels of the peritoneum are engorged. On section the lumen of the distal third is found to be obliterated by scar tissue. The remaining mucosa is normal in color but slightly thickened. Anatomical diagnosis—chronic appendicitis with partial obliteration.

Microscopic Examination. Sections are from that portion of the appendix which is bent upon itself. No lumen is present and the mucosa and submucosa are apparently replaced by very cellular young connective tissue which at one place extends down to the musculature. The remain-

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ing submucosa is composed of a fat and dense connective tissue. Close to what appears to have been the lumen are numerous areas of densely packed polyhedral cells, the nuclei of which are large, round and contain a fair amount of chromatin. No mitotic figures are present. The protoplasm is small in amount and no intercellular substance is visible. About these areas a small amount of connective tissue is present. The internal muscular layer contains numerous small, round and epithelioid cells. The blood vessels of the peritoneum are dilated. Microscopic diagnosis—carcinoma simplex of the vermiform appendix; chronic obliterative appendicitis.

These two cases with the three reported by Harte give a total of five primary cancers of the appendix observed in this laboratory during the past four years (Sept. 1, 1904 to Sept. 1, 1908) in a series of 1298 appendices removed at operation and examined microscopically. The proportion of cancer is therefore as 1 to 260 or approximately four-tenths of one per cent. If to these five are added the five reported by Elting and Baldauf, we have ten carcinomata observed in one laboratory in a period of twelve years in the routine examination of 2033 appendices, a proportion of 1 to 203, or practically one-half of one per cent.

From a review of these cases little that is new can be presented. The symptomatology if symptoms be present, is that of either acute or chronic appendicitis. The vermiform appendix having no striking function to perform, the presence of a neoplasm in the absence of inflammation would not produce symptoms pathognomonic of a physiological disturbance. The only symptom in the early stage might be pain due to pressure upon the sensory nerves or to obstruction of the lumen. The vast majority of cases in which pain was present gave, however, a history of recurrent attacks more characteristic of chronic inflammation than of carcinoma. It is noteworthy that of the thirty-two out of ninety-six cancerous appendices presenting no symptoms and removed at autopsy or during operation for other lesions, only four appeared normal to the naked eye. All others showed macroscopic changes, usually inflammatory in nature, suggesting the advisability of removal. Three of these apparently normal showed on section a chronic obliterative appendicitis in addition to carcinoma. Another argument is therefore offered for the removal, in the course of abdominal operations of every appendix showing evidence of disease.

Age plays a very important role for in youth carcinoma occurs

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with greater frequency in the appendix than in any other organ of the body. Of ninety-one cases in which the age is given, the average was twenty-nine and one-tenth years. In females it was twenty-eight and one-tenth and in males thirty and three-tenths years. The youngest was eight and the oldest, eighty-one. One may judge from the following table the frequency with which this disease occurs during the various decades of life.

3.29	per	cent.	during	the	1st decade
16.48	"	"	"	2nd	"
39.56	"	"	"	3rd	"
27.47	"	"	"	4th	"
5.49	"	"	"	5th	"
4.39	"	"	"	6th	"
0.00	"	"	"	7th	"
2.19	"	"	"	8th	"
1.09	"	"	"	9th	"

Cancer of the appendix occurs more frequently in the female than in the male. Of eighty-eight cases, fifty-four or sixty-one and three-tenths per cent. were in females whereas only thirty-four or thirty-eight and seven-tenths per cent. were in males. A possible explanation may be the greater frequency of laparotomy on the female. About one-fifth of the cancers in women were found accidentally during laparotomy for other conditions.

Numerous observations both clinical and anatomical suggest very strongly that carcinoma of the appendix is secondary to chronic inflammation. While the appendix is an organ which undergoes atrophy this apparently does not predispose it to carcinomatous change. The period of life during which these cases most frequently occur, corresponds to that of chronic appendicitis and not atrophy. Clinically, forty-seven per cent. of the cases presented symptoms of chronic appendicitis but histologically nearly all appendices were the seat of chronic inflammation. In twenty-eight per cent. also an obliterative appendicitis was present.

In this connection Ribbert's theory would appear to offer an explanation of the development of carcinoma in the appendix. In chronic appendicitis the connective tissue changes are most marked about the glands of Lieberkühn so that a portion of the cells might become detached by cicatricial contraction and continue to proliferate; or during obliteration a portion of the mucosa may become included within the scar.

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The anatomical diagnosis is usually difficult if adjacent structures are involved or metastatic nodules are present in other viscera. The appendix in twenty-three of eighty-five cases presented a tumor as it lay in the abdomen; in twenty-four the tumor was discovered after removal; in the remainder the tumor was discovered only upon microscopic examination. This emphasizes the importance of examining microscopically every diseased appendix.

The most frequent site at which carcinoma is found is the tip. Of seventy-eight cases in which the location is mentioned it involved in forty-eight the distal extremity.

Carcinoma of the appendix may be of any of the types found elsewhere in the intestines but the spheroidal cell cancer is the most frequent. Of those reported in detail sixty-one and five-tenths per cent. were spheroidal cell, thirty-six per cent. glandular, and two and five-tenths per cent. colloid.

The tumor is usually limited to the mucosa and submucosa. In only thirty of the seventy-eight analyzed did it extend to the subserosa or serosa. Infiltration is apparently along the lymphatics to the mesentery for in six cases it was most pronounced opposite the menenteric attachment and in nine the mesentery was involved.

Metastases are not often found but this may be due to the early removal of the primary growth. Metastatic growths were present in the retroperitoneal lymph nodes in two cases and in the ileo-colic in one. One case died with general metastasis and in one were multiple nodules beneath the peritoneum. The cecum was involved in only two cases.

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BENDER HYGIENIC LABORATORY.

ANNUAL REPORT OF THE DIRECTOR FOR THE YEAR ENDING AUGUST 31, 1908.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1908.

The Work of the Laboratory.—The routine examinations of all kinds are summarized in the following table: no important changes in the character of this work have occurred.

TABLE I. ROUTINE EXAMINATIONS MADE BY THE STAFF OF THE BENDER LABORATORY FROM SEPTEMBER 1, 1907 TO AUGUST 31, 1908.

	Albany Hospital.	St. Peters Hospital.	Childs' Hospital and St. Margarets House.	State Department of Health.	City Department of Health.	All other sources.	Totals.
Autopsies	42	6	2	.....	.....	84	134
Surgical Specimens	1,043	507	19	.....	.....	140	1,709
Gen. Bacteriology and Clin. Microscopy	388	92	6	3,273	2,348	227	6,334
Totals	1,473	605	27	3,273	2,348	451	8,177

Laboratory courses for undergraduates of the Albany Medical College have been given as follows:

1. Normal Histology.—Drs. Beilby and Douglas, six hours a week.

2. Pathology and Bacteriology.—Drs. Pearce, Sawyer, Hawn and Doescher, eight hours a week.

3. Clinical Microscopy.—Drs. Hawn, Sawyer and Rulison, two and a half hours a week (Dr. Laird on leave of absence).

4. Surgical Pathology.—Drs. Elting, Hacker and Sibley, two and a half hours a week.

5. Histology and Pathology, in connection with the course in Obstetrics.—Drs. Lipes and Douglas, two and a half hours a week.

6. Anatomy and Pathology of the Nervous System.—Dr. Archambault, two and a half hours a week.

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7. Experimental Physiology (Second year).—Dr. Jackson, five hours a week during first half year.

8. Experimental Physiology (First year).—Dr. Becker, two hours a week.

Among those who have availed themselves of the opportunity to work in the Laboratory for considerable periods of time are, Drs. J. A. Sampson of Albany, E. J. Buchan of Chicago, B. F. May of New York City, J. Wingate of Schenectady, W. C. Treder of Syracuse, H. H. Drake of Albany, and Messrs. Nelson Fromm, E. S. Haswell and W. A. Bing of the Albany Medical College, and L. W. Gorham and A. W. Morrison of the Johns Hopkins Medical School and Mr. George W. V. Spellacy of the New York State Department of Agriculture. These have assisted in the routine work of the Laboratory, pursued special lines of study or engaged in research work.

Investigations undertaken during the year are as follows:

1. Hacker, C. W. L., The Appearance of Glycuronic Acid in Certain Conditions of Diminished Oxidation, *Jour. Am. Med. Assoc.*, 1908, L, 252.

2. Beilby, G. E., A Clinical Study of Hypernephroma with Pathological Reports, *Surgery, Gynecology and Obstetrics*, 1908, Sept., 279.

3. Pearce, R. M., The Influence of the Reduction of Kidney Substance upon Nitrogenous Metabolism, *Journal of Experimental Medicine*, 1908, X, 632.

4. Pearce, R. M. and Sawyer, H. P., Concerning the Presence of Nephrotoxic Substances in the Serum of Animals with Experimental Nephritis, *Journal of Medical Research*, 1908, XIX, 269.

5. Sampson, J. A. and Pearce, R. M., A Study of Experimental Reduction of Kidney Tissue with Special Reference to the Changes in that Remaining, *Journal of Experimental Medicine*, 1908, X, 745.

6. Pearce, R. M., The Relation of the Adrenal Gland to Chronic Nephritis and to Arteriosclerosis: An Anatomical Study, *Journal of Experimental Medicine*, 1908, X, 735.

7. Jackson, H. C. and Elting, A. W., Clinical Notes and Physico-Chemical Study of Salt Elimination in the Urine of an Individual with General Oedema of Obscure Origin, Followed by Cure, *The Archives of Internal Medicine*, 1908, II.

8. Pearce, R. M., A Note on the Occurrence of Spontaneous

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Arterial Degeneration in the Rabbit, *Jour. of Am. Med. Assoc.*, 1908, LI, 1056.

9. Jackson, H. C., The Effect of Conditions upon the Latent Period and Rate of Aseptic Post Mortem Autolysis during the First Ten Hours, *Journal of Experimental Medicine*, 1909, XI, 55.

10. Archambault, L., The Inferior Longitudinal Bundle and Geniculo-Calcarine Fasciculus.

11. Hacker, C. W. L., Primary Carcinoma of the Vermiform Appendix with Report of Two Cases.

12. Jackson, H. C., Hawn, C. B. and Sawyer, H. P., A Study of Normal Daily Variations in the Physical and Chemical Composition of the Blood in Relation to Normal Opsonic and Phagocytic Indices (in press).

13. Jackson, H. C., Hawn, C. B. and Sawyer, H. P., The Influence of Variations in Osmotic Pressure of Blood and Serum upon Opsonic and Phagocytic Indices (in press).

14. Jackson, H. C. and Baldauf, L. K., A Chemical Study of the Liver during Fatty Transformation (in press).

15. Jackson, H. C. and Hawn, C. B., Note on the Sterility of Living Organs (Dog) (uncompleted).

16. McDonald, E., Sarcoma of the Uterus, with Report of Nine Cases.

17. Elting, A. W. and Tredway, E. E., Hereditary Gangrene in Early Life due to Endarteritis.

18. McDonald, Ellice and Krieger, W. A., Bilateral Tubal Pregnancy, with Report of Two Cases.

19. Hacker, C. W. L., Carcinoma of the Umbilicus.

20. Archambault, L., Contribution to the Anatomy and Pathogeny of Angenesia of the Corpus Callosum.

Of these investigations, the third to sixth inclusive and the eighth, ninth, twelfth, and fourteenth were conducted under grants made to the Director and Dr. H. C. Jackson by the Rockefeller Institute for Medical Research; the first, seventh and thirteenth under similar grants from the Committee on Scientific Research of the American Medical Association.

Changes in the Staff.—The changes in the staff this year are quite general. My own resignation takes effect September first, in order that I may accept the Professorship of Pathology at the New York University and Bellevue Hospital Medical College of New York City. Drs. H. P. Sawyer and C. B. Hawn termi-

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nate their connection with the Laboratory on August 31st; the former accompanies me to New York to become Instructor in Pathology in the New York University and Bellevue Hospital Medical College; the latter enters general practice in Albany. To one of these vacancies has been appointed M. D. Cronin (M. D., Albany Medical College, 1907); the other has not yet been filled. Dr. C. W. L. Hacker resigned June 1st to enter private practice and has been succeeded by J. L. Bendell (A. B., Yale, 1903, M. D., Albany Medical College, 1907). Dr. T. F. Doescher resigned July 1st to become an assistant to Dr. Albert Vander Veer and in his place has been appointed L. H. Gaus (M. D., Albany Medical College, 1907). R. C. Keigher (M. D., Albany Medical College, 1907) has been appointed Pathological House-Officer by the Board of Governors of Albany Hospital to succeed Dr. W. A. Krieger, who resigned July 1st to accept the position of Pathologist to the Vassar Hospital of Poughkeepsie, N. Y.

Work of the Past Five Years.—As this report marks the completion of my five years' service as Director, I append a table showing the activities of the laboratory during this period. This table with that which appeared in my Third Annual Report (1906) represent graphically the work and development of the laboratory since its opening in 1896.

TABLE II. SUMMARY OF WORK OF PAST FIVE YEARS, 1903-1908.[1]

	1904	1905	1906	1907	1908	Totals	Average
Autopsies	123	129	120	135	134	641	128
Surgical Specimens	1,003	1,271	1,471	1,617	1,709	7,071	1,178
Gen. Bacteriology and Clin. Microscopy	2,515	2,683	2,961	5,725	6,334	20,218	4,043
Totals	3,641	4,083	4,552	7,477	8,177	27,930	.....
Laboratory Courses	6	6	6	8	8	.....	.....
Publications	11	8	17	12	11	.....	.....

Worthy of special mention is the development of the Department of Physiological Chemistry under the able direction of Dr. H. C. Jackson. This department, established three years ago, has been of great value in connection with the routine work and has added vastly, as may be seen in the titles of published investigations, to the possibilities of co-operation in research work. Dr. Jackson's relation to the laboratory work, both routine and experimental, has been very intimate and has made it possible to

[1] Each yearly period ending August 31st.

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apply to any problem the methods of physiology and chemistry in addition to those of pathology and bacteriology.

I therefore take this opportunity to express my appreciation of the great value to the laboratory of Dr. Jackson's work and also of his very cordial co-operation during the past three years. Moreover I would suggest to your board the appointment of an additional assistant to aid in the further development of this very important aspect of laboratory effort.

The Bender Laboratory Club.—This organization continues to be a most important feature of the laboratory life. The guests during the past year were Dr. Warfield T. Longcope, Director of the Ayer Laboratory of the Pennsylvania Hospital of Philadelphia who discussed our newer knowledge of Hodgkin's disease and Dr. Henry A. Christian, Assistant Professor of Medicine at the Harvard Medical School, who presented a general review of recent work on "Experimental Nephritis."

"Studies from the Bender Laboratory."—The fifth volume of this laboratory publication will appear at the end of the present year. In the first volume (1904) was incorporated a short sketch of the history of the laboratory together with a list of previous publications under Dr. Blumer's directorship and portraits of the founder and the first director. In this, as in succeeding volumes, all papers published from the laboratory have been reprinted in full and in each also the annual report of the director, summarizing all activities of the laboratory, changes in staff and other items of interest, has appeared. These volumes thus present, in complete form, the work and publications of the laboratory and constitute as well a general history of the institution. They have been so favorably received that it is to be hoped that your board will see its way clear to continue this annual publication.

Gifts.—It is a great pleasure to acknowledge the financial support which has been rendered by Drs. Albert Vander Veer, Henry Hun, W. G. Macdonald, Arthur W. Elting, A. H. Traver and C. F. Theisen. These gentlemen have contributed funds which have been used for special assistants in surgical pathology and neuro-pathology, for apparatus, and to a small extent for defraying the expenses of the last volume of "Studies from the Bender Laboratory." To Dr. Henry Hun we are also indebted for a set of lower power lenses for use with the microscope attachment of the projection lantern. This very general assistance, which may be taken as an appreciation of the usefulness

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of the laboratory, argues well for its support and development in the future.

Finally, as this report marks the end of my directorship, I wish to express my appreciation of the interest which your board has always shown in the work of the laboratory as well as of your ready co-operation in the development of its activities. The five years during which I have been associated with the Bender Laboratory have been most helpful to me and represent a period of my experience as pathologist to which I will always look back with the greatest pleasure and satisfaction. If, on the other hand, I have helped you, as I sincerely hope I have, to develop the influence of the Bender Laboratory and to advance the spirit of scientific medicine in Albany, there will be the added satisfaction that others than myself have profited by our mutual efforts.

Respectfully submitted,

RICHARD M. PEARCE,

August 31, 1908. ***Director.***

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ROBERT G. SCHERER

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In Memoriam

Robert G. Scherer was born in Albany, N. Y., March 20, 1861, his father being a prominent merchant of that day. His education was obtained in the public and private schools of this city and in his father's store and at the Commercial College he received a thorough business training. Adopting law as his profession, young Scherer at an early age entered, as clerk, the law office of Paddock, Draper and Chester. After several years spent in this office he attended Cornell University and was graduated from Columbia Law School. About 1881 he formed a law partnership with John F. Montignani which continued for some years. On the dissolution of this firm he was associated with J. Murray Downs and Neile F. Towner. In 1884 he married Anna, daughter of James T. Story of Albany, N. Y., and she with one daughter survive him. In 1898 he was appointed Miscellaneous Court Reporter and so well was his work in this position approved by his profession that his reappointment in 1903 was received with entire satisfaction.

As a lawyer Robert G. Scherer was highly esteemed. He appeared frequently at Special Term and in the Appellate Division and Court of Appeals. He was widely known as a counsellor and adviser in matters of public and private business. Few men of his years in so arduous and exacting a profession accomplished more or attained such eminence.

Mr. Scherer was a Republican; a member of the Board of Public Instruction of the City of Albany from 1885 to 1889 and introduced many reforms in the school system; a member of Assembly from Albany County in 1896 and 1897 and Chairman of the Judiciary Committee; and a member of the Committee on Law Reform of the State Bar Association. He was a prominent Mason.

The characteristics that won for Robert G. Scherer social, political and professional prominence were his thoughtfulness, thoroughness and efficiency. He was of a quiet and almost retiring disposition but possessed a charm of manner and cheerfulness of temperament with a natural kindliness of heart that made him always friendly, affable and genial.

Mr. Scherer's admirable qualities were best illustrated by the fact that although his life was filled to overflowing with varied

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work and manifold interests connected intimately with his professional and public activities he gave freely of his time and intelligence to the management of the Albany Hospital with which institution he was for many years connected and of which he was a Governor at the time of his decease.

In the encouragement of medical science as in all matters philanthropic, Mr. Scherer manifested the greatest interest. This drew him into heartiest collaboration with Mr. Matthew Bender, the founder of the Bender Hygienic Laboratory for which institution he prepared the constitution and by-laws. He served as President of the Trustees of the Laboratory from February 23, 1904 until his death.

After a lingering illness Mr. Scherer died at his home on Madison Avenue in this city on October 28, 1905 at the early age of forty-four years.

As a tribute of their respect for their late President the Trustees of the Bender Hygienic Laboratory passed the following resolution and placed it upon the minutes.

By the sad and untimely death of Robert G. Scherer, which occurred at his home November 1, 1905, the Board of Trustees of The Bender Hygienic Laboratory lost one of its most valued and faithful members.

Mr. Scherer has been identified with the Bender Laboratory since its inception. As a friend and the attorney of Mr. Matthew Bender, the donor of the Laboratory Building, Mr. Scherer advised with and aided in directing and carrying out Mr. Bender's wishes in the erection of the Laboratory. In securing from the City of Albany the site and in the organization of the corporation, Mr. Scherer took the most active part. He met with us at the organization of the Board June 27, 1905, and has been in continuous service on the Board since—acting as its legal adviser and performing all other duties pertaining to his trusteeship with the deepest interest and fidelity, and we record to-day the expression of the high esteem and regard in which he was held, and our appreciation of his valued services on the Board.

We direct, by resolution, that a copy of this record be mailed to his bereaved family, together with the expression of our deepest sympathy to them in this hour of their great sorrow.

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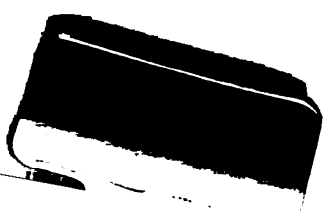

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